ANNUAL REVIEW OF MEDICINE

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VOLUME 8

1957

ANNUAL REVIEWS, INC.
PALO ALTO, CALIFORNIA, U.S.A.

ANNUAL REVIEWS, INC.
PALO ALTO, CALIFORNIA, U.S.A.

FOREIGN AGENCY

Maruzen Company, Limited
6 Tori-Nichome Nihonbashi
Tokyo

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PRINTED AND BOUND IN THE UNITED STATES OF AMERICA BY
GEORGE BANTA COMPANY, INC.

PREFACE

We are pleased to record again our debt of gratitude to those authorities in their respective fields who, at our invitation, have prepared the accompanying chapters in this *Annual Review of Medicine*. We trust and expect that their thoughtful surveys will be appreciated by all who examine the sea of contemporary medical literature.

Lack of space has forced the omission of the excellent chapter "Annotated List of Reviews in Medicine" customarily contributed by E. M. MacKay and L. MacKay. Unfortunate circumstances postponed the preparation of a review on neoplastic diseases by C. Oberling.

We wish to pay our respects to the memory of G. Lyman Duff, who was our colleague all too briefly, and of John P. Peters, who was to have contributed to this volume.

Finally, we thankfully acknowledge the helpful services rendered by Editorial Assistants Mrs. Delores G. Ward, Mrs. Marjorie Jones, and Miss Janice Young.

W.C.C. R.M.
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VOLUME 9 (IN PREPARATION)

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ADRENOCORTICAL HORMONES AND THE MANAGEMENT OF INFECTION[1]

By Edward H. Kass, M.D. and Maxwell Finland, M.D.[2]

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The relationship of adrenocortical hormones to resistance to infection has been reviewed previously in these volumes (1, 2), and noteworthy reviews of various aspects of the problem have appeared since (3 to 6). The present review will concern itself with but one aspect of the problem: the place of adrenal steroids in the management of infectious diseases. Many contributions to the problem have already been reviewed by the authors (2) and will not be discussed in detail here.

Depression of Host Resistance by Corticosteroids[3]

Experimental.—The evidence that large doses of cortisone (11-dehydro, 17-OH corticosterone), cortisol (hydrocortisone, 17-OH corticosterone) or corticotropin (ACTH) generally depress resistance to infection in man and in experimental animals is substantial (1 to 6). Additional documentation of this effect in experimental animals has appeared. Depression of resistance has varied in different animal species, and with different dosage schedules and experimental designs, but to the large list of agents and hosts (2) can be added several additional examples of depression of resistance by adrenocortical steroids in bacterial (7 to 13), rickettsial (14, 15, 16), viral (13, 17 to 23), mycotic (10, 24 to 28), protozoal (29, 30), and helminthic (31, 32) infections in mice, guinea pigs, rabbits, rats and monkeys. Particularly noteworthy were the observations of Denny & Thomas (12) who showed that the administration of cortisone as late as 104 days after the acute infection caused recrudescence of group A streptococcal infections in rabbits with fatal outcome. The experiments indicate asymptomatic persistence of the organisms in the tissues of the animals as well as the profound effect of cortisone.

Attempts have been made to utilize this effect for diagnostic and other special purposes (2). For example, it is now a well-established practice in the preparation of poliomyelitis vaccine to utilize cortisone-treated monkeys in

[1] The survey of the literature pertaining to this review was completed in June, 1956, but many journals for 1956, particularly foreign ones, were not available. The review is intended as a critical analysis; no attempt has been made, in the space allotted, to present a complete summary of the pertinent literature.

[2] Studies by the authors and their co-workers cited in this paper were aided by a grant from the National Institutes of Health.

[3] For convenience, the term corticosteroids will refer to cortisone and cortisol unless otherwise indicated, and it will be assumed that the ultimate effects of administering corticotropin will be similar to those of giving these two steroids, with exceptions that will be discussed.

testing for the presence of active virus (33, 34). Jørgensen & Ringsted (35) attempted to accelerate the routine diagnosis of tuberculosis by using cortisone-treated guinea pigs, and found that the incidence of tubercles was somewhat greater in cortisone-treated than in control animals four weeks after inoculation, but the results were not sufficiently striking to warrant routine use of the method. Toolan (36) reported that pretreatment of hamsters with cortisone facilitated the transfer of human embryonic tissue to the hamster cheek pouch, and subsequent tissue cultures from such transfers were more readily made than when cortisone had not been used. Dunham & Ewing (37) have suggested that it may be possible to facilitate the adaptation of poliomyelitis virus to chick embryos by injection of cortisone into the yolk sac.

A few observations have suggested that an adverse effect may not necessarily follow the use of corticosteroids or corticotropin. For example, Weimer *et al.* (38) found that when tuberculous guinea pigs were treated for three weeks with cortisone or corticotropin, and examined $6\frac{1}{2}$ weeks later, there were no significant differences between hormone-treated and control animals. When BCG (Bacillus Calmette-Guérin) was injected into cortisone-treated guinea pigs (39) the resistance of these animals, as tested by later challenge with virulent tubercle bacilli, was greater than in controls.

These two experiments suggest that because the guinea pig is ordinarily so highly susceptible to virulent tubercle bacilli there is little native immunity to depress. Under such circumstances treatment with cortisone might permit more rapid multiplication of the bacilli and earlier dissemination, but if one or two bacilli cause a lethal infection, and if a sufficient period of time is allowed to elapse, there should be no difference between cortisone-treated and control animals. The studies of Jørgensen & Ringsted (35) are consistent with this interpretation. Similarly, when avirulent organisms such as BCG are injected into the normal guinea pig, multiplication is limited for there is some native immunity to these organisms. Hence it would be anticipated that cortisone would permit greater multiplication of the bacilli with the consequent accumulation of greater amounts of antigen, which would increase the immunity of the host if the cortisone were then discontinued. It is noteworthy that cortisone did not depress resistance sufficiently to permit the BCG to become virulent for the guinea pig.

Clinical.—Even a cursory review of the literature of the past three years has yielded ample additional evidence that infections constitute one of the important hazards of the prolonged use of corticosteroids clinically, the hazards being compounded by the frequent masking of symptoms and signs of infection (40 to 61). Indeed, hardly a series of cases treated with corticosteroids has been published in which prolonged treatment with these agents has not been related to the appearance of severe infections in some of the patients. There have appeared, in relation to the administration of corticosteroids, instances of pneumococcal and Friedlander's bacillus pneumonia (40, 53, 54), moniliasis, blastomycosis, and other mycoses (26, 41, 47, 48,

57, 61), tuberculosis (43, 44, 47, 50, 59), meningitis (45), malaria (51), infections with unusual saprophytes (49), and staphylococcal endocarditis (56). When infections were already present, corticosteroids failed to benefit even those patients with chronic asthmatic bronchitis who were wheezing (58, 60). Particularly sobering is the report of Haggerty & Eley (46) that there have been at least 12 fatal cases of varicella in children who were receiving adrenocortical hormones at the time of exposure to the disease.

The magnitude of the hazard from infection during the clinical use of corticosteroids cannot be judged accurately at present, since much of the literature is concerned with selected case groupings and, of course, the various groups of patients under study differ widely in composition, underlying illness, degree of prophylactic therapy, etc. A few general observations appear warranted:

(*a*) The hazard is small but significant. Eighteen of 210 patients with various primary diseases developed moniliasis; the disease was relatively mild in 11 and might have gone unrecognized without special awareness and means for laboratory diagnosis (41). Similarly, of 69 rheumatic children receiving corticotropin or cortisone and procaine penicillin, there was one instance of purulent meningitis, an extensive abscess at a site of injection, and several milder illnesses presumably of infectious origin (45). The appall ing occurrence of fatal varicella in children receiving corticosteroids (46) was collected after a poll of 65 physicians, many of them teachers in large academic centers in the United States, Canada and England, so the figure cited represents the culling from an unusually large experience. Benedek & Montgomery (42) did not believe that the incidence of infection was unusually high in their patients, in a smaller experience. Relatively low incidence of serious infections can be surmised from other reports in the literature, only a few of which have been selected (52, 53, 54, 61, 62).

(*b*) It would seem reasonable to believe, with but limited supporting evidence, that the hazard attributable to intercurrent infection when corticosteroids are being administered is relatively great in chronic diseases such as disseminated lupus erythematosus, sarcoidosis, etc., in which the possibility of underlying chronic infection is great under ordinary circumstances, and in which there may be sufficient debility to render patients more susceptible than usual to infections (48, 50). Conversely, in acute self-limiting diseases, or in acute illnesses with prolonged convalescence, where debility is not prominent, the hazard may be somewhat less.

(*c*) The prophylactic use of antibiotics such as penicillin might conceivably protect against highly susceptible organisms such as group A hemolytic streptococci or pneumococci, but would offer relatively limited protection against antibiotic-resistant staphylococci, Gram-negative rods, or against the granulomatous infections. The infections occurring in patients who are receiving prophylactic penicillin support the validity of the statement (45, 52, 54).

(*d*) When live viruses were inoculated into cortisone-treated patients

with advanced malignant disease in the hope of inducing destruction of the neoplasms, the numbers of resulting infections and the duration of the viremia were but slightly higher than in controls (63).

Use of Corticosteroids with Antimicrobial Agents in Infection

The effects on resistance to infection when antimicrobial drugs are used in conjunction with corticosteroids may be summarized briefly as follows:

(*a*) When cortisone, cortisol or corticotropin are used in conjunction with antimicrobial therapy, the hormones generally reduce the effectiveness of a given dose of antimicrobial agent, and, conversely, when sufficiently large doses of antimicrobial drug can be given, the adverse effect of a given dose of corticosteroid on the host can often be overcome (1 to 5, 64 to 73).

(*b*) If the antimicrobial drug has limited effectiveness because of its mode of action, toxicity, or other mitigating factors, the adverse effects of the corticosteroids are readily demonstrable (66, 69, 70). For example, the protective activity of penicillin in pneumococcal infections in mice or rats is diminished by corticosteroids, but this effect is easily overcome by increasing the dose of penicillin (2, 65, 69). If, however, tetracycline or chloramphenicol is used, the adverse effects of corticosteroids are less readily overcome, since these antibiotics are more toxic than penicillin and are bacteriostatic (66, 69).

(*c*) As might be anticipated, the adverse effect of corticosteroids on resistance to infection is more readily overcome by antibiotics in hosts with high native resistance to the microorganism involved. Rats and rabbits, with high resistance to tuberculosis, may be made more susceptible by the use of cortisone or corticotropin, but the effect is readily overcome with small amounts of streptomycin. In tuberculous guinea pigs, on the other hand, it is difficult to overcome the adverse effect of cortisone even with large doses of streptomycin (4, 71).

Despite the many experiments involving the combined use of antibiotics and corticosteroids only two observations suggest that the combination may produce a more favorable outcome than follows the use of antibiotics alone (74, 75), and in neither instance is the effect particularly striking. Further observations along these lines are clearly warranted.

Clinical observations.[4]—It has already been suggested that the resistance of most human beings to infection is not readily depressed by the use of corticosteroids. If specific antimicrobial agents are used in addition, a relatively extensive and carefully controlled series of observations becomes essential in order to assess relative hazard as opposed to relative gain in the use of corticosteroids. Few observations on the treatment of infection with corticosteroids and antibiotics are sufficiently well controlled to contribute substantially to a solution of the problem. Patients with tuberculosis have

[4] Infections in which adrenal insufficiency is presumed to play a major role are discussed separately.

been given corticotropin or cortisone along with antituberculous drugs without apparent harm (4, 5, 76, 77, 78). Occasionally, desirable secondary effects have ensued: clinical manifestations of hypersensitivity to effective antimicrobial drugs have been suppressed by the use of cortisone and antimicrobial therapy could be given with clinical benefit (79, 80). Similarly, many attempts have been made to treat tuberculous meningitis with corticosteroids with the hope of minimizing the incidence of spinal block and late fibrotic complications. The data here, too, are difficult to analyze because of the lack of adequately controlled observations. In the management of tuberculosis, isoniazid was introduced at almost the same time as the use of corticosteroids; it is, therefore, difficult to judge how much of a contribution the corticosteroids have made (4, 5, 81 to 85). In one controlled study involving 30 patients, no effect in either direction was found following the addition of cortisone to standard antituberculous treatment, although most observers, on the basis of uncontrolled studies or small series, have felt that corticosteroids were beneficial. An instance of purulent meningitis occurring in a patient treated with corticotropin and antituberculous drugs has been reported (83).

In the management of typhoid fever and rickettsiosis (2, 5, 86, 87, 88) rapid defervescence follows the combined use of corticosteroids and appropriate antibiotic treatment. Many workers have felt that no hazard has been introduced and that distinct symptomatic benefit has resulted. On the other hand, relapses have been observed in patients receiving combined steroid and antibiotic therapy, and it is still not clear whether the symptomatic response here, too, has hidden some adverse effects on resistance. An apparently direct relationship between the duration of cortisone treatment and the occurrence of relapses in acute brucellosis has been observed in a small series of cases (89); the administration of cortisone for only three or four days produced favorable symptomatic effects and did not appear to be particularly harmful in that series. The problems are similar in other infections (90, 91).

Jahn *et al.* (92) have published data in support of the vigorous statements from their clinic (93, 94) that corticosteroids and corticotropin are of benefit in severe infections. These data consist of 42 patients with so-called "medical" infections and 41 with "surgical" infections who were treated with corticosteroids and antimicrobial drugs. The authors present their data and list their estimate of the value of using corticosteroids in the management of the infections. In the "medical" group were 14 cases of meningococcal infection, with 4 deaths. There were four children under 18 months of age, the age group with the highest mortality from this disease, and three of these four children died. Of the 14 patients, the authors considered that only two had a "definite" benefit from the use of corticosteroids, and three had a "probable" benefit; one of the "probables" died. There were six cases of nonmeningococcal meningitis, two of which were fatal. Three of the six meningitides were attributable to *H. influenzae*, and two of the patients experienced a slow and one a rapid defervescence, an experience which, although too

small to be evaluated, can hardly be considered unique. In all, there were 12 deaths among the 42 "medical" patients; among them were two who were listed as having experienced "probable" benefit initially from corticosteroids, and one dead patient was thought "definitely" to have been benefited.

Of the 41 patients with "surgical" infections, 17 died; four of the latter are regarded as having "probably" been benefited by the use of corticosteroids, and two as having experienced "definite" benefit. The best results were in the group of patients with ruptured appendices; the group included no infants and only two adults, only one of whom was over 65 years of age. There could hardly be a more favorable group for the treatment of ruptured appendix, and it is likely that the same results would have been obtained without the use of corticosteroids. The poorest results were obtained in the patients that offered the most difficult clinical problems, patients with perforated viscera and breakdown of resections. No evidence of benefit from hormonal treatment was obtained in these patients. This study is reported in detail here to emphasize the great difficulties in evaluating the results of combined hormonal and antibiotic treatment, unless simultaneous comparisons are made with the effects of antibiotics alone. The results obtained in this study hardly constitute impressive evidence that corticosteroids were life-saving in the patients with infection.

A carefully controlled study was conducted by Wagner *et al.* (95) who compared cortisone and penicillin with penicillin alone in the management of pneumococcal pneumonia. They observed more rapid defervescence and general symptomatic improvement in patients receiving cortisone and penicillin, but one cortisone-treated patient developed prolonged hypothermia and renal insufficiency. Hypothermia has been reported as a complication of cortisone therapy (96). The amounts of penicillin that are used in the contemporary management of pneumococcal pneumonia are far in excess of the minimal effective amounts, and the excess that was used in this study was, in all likelihood, sufficient to overcome even a substantial reduction in host resistance. The results of treatment of pneumococcal pneumonia with penicillin are, of course, so good that an enormous series would be necessary to determine whether cortisone exerted any small adverse effect on morbidity or mortality. It is evident that there was no major adverse effect. The study is an important one, however, in providing a setting for future exploration of the problem.

There are numerous case reports of apparently favorable symptomatic responses to the use of corticosteroids in many other infections (e.g., trichinosis, infectious mononucleosis, etc.). Most of these are infections with very low mortality rates and with few complications; presumably, in such cases, host resistance may be depressed considerably without much untoward clinical effect. It will be difficult to collect a sufficiently large and adequately controlled series of such diseases to determine whether there is ultimate good or harm in the use of corticosteroids.

The relatively frequent occurrence of infectious hepatitis among military

personnel has provided a source of material for careful study. Evans *et al.* (97) have shown clearly that whereas corticosteroids brought about rapid symptomatic improvement, increased appetite, and rapid fall in serum bilirubin, the relapse rate in hormone-treated patients was 20 per cent as compared with no relapses in control patients. Giving human serum gamma-globulin with cortisone did not diminish the incidence of relapse. The authors concluded that despite the symptomatic improvement, cortisone therapy had no place in the management of infectious hepatitis [see also Sborov *et al.* (98)]. Rapid subsidence of the orchitis of mumps has been observed after the use of cortisone (91, 99, 100); it will be of interest to determine the ultimate effect of such treatment on sterility.

These selected data illustrate the difficulties in determining the place of a drug such as cortisone in the management of infections. Further studies will undoubtedly be oriented in two directions: (*a*) attempts to show that corticosteroids do no harm in a given situation but provide welcome symptomatic relief, and (*b*) attempts to show that corticosteroids may, under proper conditions, augment host defensive mechanisms.

The former aspect, that of symptomatic relief, is not to be minimized. However, there are better understood and potentially less troublesome drugs that provide such relief. Controlled studies of the comparative effects of aspirin and corticosteroids in rheumatic fever and rheumatoid arthritis showed no important differences in the effects of these two drugs on the course of the disease (101, 102, 103). Therefore, in infections in which it is argued that corticosteroids have done no harm but have provided symptomatic relief, it may be appropriate to compare common analgesics with corticosteroids.

It is of even greater importance, however, to determine whether corticosteroids augment host defensive mechanisms.

Protective Effects of Corticosteroids in Infection

Five lines of investigation have suggested a possible beneficial role of corticosteroids in mechanisms of resistance to infection. These are as follows: (*a*) the protective action of corticosteroids in adrenal insufficiency, (*b*) the protective action of small amounts of corticosteroids, (*c*) the possibility that other steroids or other biologically active substances may overcome some of the actions of cortisone or cortisol, (*d*) the protective action of corticosterone against endotoxin, and (*e*) the potentiation by corticosteroids of the action of vasopressor agents.

Adrenal insufficiency.—In manifest adrenal insufficiency, the protective role of corticosteroids in restoring resistance to normal levels is well established and has received substantial affirmation recently in mice (65, 104) and in man (105). For example, the increased susceptibility of adrenalectomized mice to influenza virus or to pneumococci may be returned to control levels by doses of cortisone that are larger than the minimal maintenance

dose for uninfected animals. Still larger doses of cortisone decrease resistance to infection (unpublished observation).

There is no doubt that corticosteroids are life-saving in patients with Addison's disease who have developed infections (105). The difficult problem is to assess the frequency with which adrenal insufficiency occurs in the course of severe sepsis in patients who have not shown evidence of pre-existing adrenal insufficiency. There is also evidence that vascular collapse occurring during the course of sepsis is usually not a result of adrenal insufficiency (106). Circulating hydroxycorticoid levels in 12 patients with collapse attributable to sepsis of various etiologies were usually above the normal range, and none was in the low normal or frankly Addisonian range (unpublished observation).

In collapse associated with meningococcemia, the high incidence of adrenal hemorrhage has naturally suggested that adrenocortical insufficiency is present and that large doses of adrenocortical hormones may be lifesaving. However, it should be emphasized that there are few controlled, objective data to confirm this impression. Thus, although there are several case reports of recoveries from meningococcemia with severe hypotension and purpura, the patients have usually been treated with specific antibacterial drugs, vasopressor agents, and general measures to combat collapse, as well as with corticosteroids (107 to 114). Despite this, there have been failures (115, 116, 117). The largest series of cases of meningococcal infection reported in recent years is that of Tobin (117); of the 63 cases reported, 9 were considered to have Waterhouse-Friderichsen syndrome and 5 of these survived. The effects of cortisone, according to Tobin, were "not spectacular." The experience of Jahn *et al.* (92) has been referred to previously and does not indicate any impressive benefit from adrenal steroids in this syndrome. During the past year, the authors have observed three cases of meningococcemia with vascular collapse in which treatment with norepinephrine and sulfadiazine without resort to adrenocortical hormones, resulted in recovery.

A controlled study of the value of corticosteroids in meningococcemia is urgently needed. There are highly effective antibacterial drugs available; there is also evidence that vascular collapse may be treated with some success by vasopressor agents (118, 119), and the possibility exists that the effectiveness of antibacterial therapy may be diminished by the use of corticosteroids. Although, in the experimental situation, the toxic effects of meningococcal endotoxin may be diminished by pretreatment of the test animal with corticosteroids (*vide infra*), not all animal species show this effect, and the administration of steroids after endotoxin has been given is without apparent beneficial effect. Furthermore, the pretreatment of young rabbits with cortisone may cause them to develop bilateral renal cortical necrosis in response to a single intravenous dose of meningococcal toxin (6). It should also be recalled that just one generation ago spectacular results in the management of meningococcemia were claimed for quantities of adrenal cortical extracts that by today's standards would be considered to make only a negligible contribution to the body pool of corticosteroid.

Acute adrenal insufficiency may occur for reasons other than hemorrhage. The phenomenon of adrenal exhaustion is much written about but difficult to document. Tubular degenerative changes and frank hemorrhages, such as may appear in the adrenal cortex in fatal infections and in circulatory collapse, can be reproduced in rats by the administration of corticotropin (120, 121), but there is no clear evidence that these histologic changes are indeed associated with a diminished output of steroid. Tubular changes suggesting "exhaustion" were found in the adrenal cortices of 9 of 96 adrenals taken from children at autopsy, and occurred in pyogenic infections and in neoplastic disease (122).

Another possible basis for adrenal insufficiency has been suggested by the observations of Rosenfeld (123) who found that endotoxin, perfused through calf adrenal glands, inhibited steroidal synthesis. Whether such a situation obtains in bacteremia with endotoxin-containing bacteria is not clear, since the normal or elevated blood levels of steroid that have been observed in such bacteremias may reflect interference with peripheral utilization and clearance rather than with normal steroidogenesis (124).

Direct adrenal damage may also occur as a consequence of the action of diphtheria toxin. However, the administration of cortisone, which may protect the adrenal cortex from the hemorrhage ordinarily caused by diphtheria toxin, does not thereby increase the life expectancy of the test animal (2, 125). In relation to this problem, Tonutti (126) has observed that hypophysectomy also prevents the adrenal hemorrhage caused by diphtheria toxin but that endotoxin induces hemorrhagic changes in the adrenal cortices of hypophysectomized as well as intact animals. It is thus apparent that a metabolically active adrenal cortex is not necessary for endotoxin to affect it adversely.

Acute adrenal insufficiency may occur when exogenous steroids have suppressed endogenous steroidogenesis, and an added demand for corticosteroids has been imposed (127, 128, 129). However, acute adrenal insufficiency is often implicated unjustly when the deterioration of the patient is a result of unrecognized sepsis, electrolyte disturbances, etc. (130). The paradox in this situation is that when relative adrenal insufficiency is thought to be present because infection has supervened during prolonged corticosteroid therapy, it has generally seemed prudent to give corticotropin to stimulate endogenous secretory activity and also to increase the dose of exogenous steroid to overcome the postulated relative insufficiency. The details of this procedure are entirely pragmatic at present, but with the advent of more simplified methods for measuring circulating corticosteroid levels it should be possible to arrive at a more objective basis for determining dosage levels that are adequate without being excessive.

In summary, the frequency of acute adrenal insufficiency as a consequence of sepsis is not known, but it appears to be uncommon. Although treatment of suspected adrenal insufficiency during severe infection is widely practiced, there is little objective basis for deciding whether to use corticosteroids and how much to use. There are arguments for and against the use of corti-

costeroids in meningococcemia, and only carefully controlled clinical study is likely to resolve the dilemma.

Optimal dose of corticosteroids.—Although most approaches to the use of corticosteroids in the management of infections have involved large doses of hormone, there are suggestive experiments in which cortisone has augmented resistance to infection when given in doses that are much below those that are generally employed in treatment (69, 131, 132, 133). One explanation of this phenomenon which has been advanced (5) is that severe infection may induce mild relative adrenal insufficiency that is overcome by the administration of small amounts of steroid. Since corticosteroid levels in the blood are usually elevated in infections, it must be postulated that (*a*) insufficiency is rare, or (*b*) it is a species specific phenomenon, or (*c*) there is a block to steroidal activity or transport as a consequence of the infection, and small increases in the blood level may facilitate the passage of steroid into host cells. The vagueness of the considerations involved is attributable in large part to the absence of clear concepts concerning the mechanisms of hormonal action (134), and attests to the need for study of these problems at a pragmatic clinical and laboratory level while continuing investigation of mechanisms of action of adrenal steroids. There are at present no clinical counterparts to the laboratory observations that small doses of corticosteroid may confer increased resistance to infection.

Possibility that other biologic substances may overcome the effects of corticosteroids.—This speculation is based on a few interesting observations. Under certain circumstances corticotropin has failed to depress resistance to infection although it has induced general metabolic changes of comparable magnitude to those produced by depressant doses of cortisone or cortisol. This phenomenon has been observed in mice and hamsters (2, 10, 13). In addition, Smith and co-workers (73, 74) found that certain doses of corticotropin failed to alter the course of experimental tuberculosis in rabbits although these doses exerted greater lympholytic effects than did doses of cortisone that depressed resistance. Similarly, amounts of corticotropin that exerted but slight effects on antibody production caused greater losses of weight in the rabbits than did amounts of cortisol that markedly suppressed the antibody response (135).

A partial explanation for these findings may lie in differences in the content of the adrenal secretion (136). The nature of the adrenal secretion varies in different animal species, and, under certain circumstances, in the same species as well (136 to 139). Corticosterone or cortisol or both are predominant adrenal steroids of all animal species that have been studied, but corticosterone is less active than is cortisol in depressing resistance to infection (2, 9, 13) and antibody formation (135). Although cortisol is usually the predominant adrenal steroid in man, corticosterone is secreted and may be the predominant steroid at times (140, 141). Corticosterone does not inhibit the action of cortisol on antibody formation (135), but there is some

evidence suggesting that variations in the relative amounts secreted may alter some aspects of host resistance. In addition, certain rabbits have responded to tuberculosis by producing relatively large amounts of corticosterone, whereas corticotropin, given to uninfected rabbits of the same genetic background, stimulated the secretion of a smaller total output of steroid but relatively more cortisol than did the infection (139).

In comparing the effects of corticosterone, cortisol and other related steroids, it is necessary to take into account some evidence that corticosterone is mobilized from tissue sites of deposition much more rapidly than is cortisol (142) and that these substances, as well as some newer derivatives of cortisone and cortisol, differ markedly from one another in terms of their absorption and turnover in the body (140, 143 to 146). Thus, some of the reported differences in metabolic activity of the various steroids may require revision as this variable is controlled. It is conceivable that still more potent anti-inflammatory substances will be found which have been overlooked in the usual screening procedures because they were mobilized too rapidly from the sites of deposition. It is noteworthy that analyses of adrenal vein blood invariably give evidence of the presence of several substances in trace amounts, and the identification and biologic characterization of most of these have not yet been achieved.

Other hormones and nonhormonal substances have been reported to overcome some of the adverse effects of corticosteroids. Somatrophic hormone has been reported to do so, but the evidence is highly contradictory (2, 7, 13, 147 to 150). Aldosterone, the newest adrenal steroid to be identified [see review by Gaunt *et al.* (151)], exerts antagonistic effects to cortisol locally (152, 153) and in one highly suggestive study by Meier & Bein (154) was active in maintaining vascular tone under conditions in which cortisol, deoxycorticosterone, corticosterone and corticotropin failed.

Attempts have been made to overcome some of the actions of cortisone by the use of liver extracts, vitamin B_{12}, and choline (155, 156), but the interpretations of the original data have been challenged (157, 158) and it seems unlikely that these will prove to be useful approaches.

It is possible that there will be, in the future, hormonal or other metabolic means for controlling or counteracting some of the adverse effects of cortisone and cortisol on resistance to infection. At present, however, none of these possibilities has been explored sufficiently to permit an assessment of their significance.

Protection against endotoxin.—The protective effect of cortisone against the lethal action of endotoxin is well documented and striking. Beck & Voloshin (159) observed that cortisone and adrenal cortical extract protected experimental tumors against the necrotizing effect of endotoxin, and Chedid *et al.* (160) achieved protection against the lethal action of endotoxin by pretreatment of the experimental animal with cortisone. It was also shown that cortisone and corticotropin were antipyretics and that under proper

circumstances the Shwartzman response to endotoxins was attenuated (1, 2, 3, 6, 161). Certain of these relationships have been more clearly defined and may be summarized:

(*a*) Cortisone protects mice, rats, guinea pigs, rabbits and chick embryos against the simultaneous or subsequent injection of lethal doses of bacterial endotoxin (160 to 165). (*b*) The protective effect is apparently dependent upon the presence of increased blood levels of corticosteroid at the time that the endotoxin is administered. When hormone is given one-half or one hour after the administration of endotoxin, the protective effect is diminished or absent (142, 163, 165). (*c*) Cortisol also protects against endotoxin, and corticosterone intravenously is about as protective as is cortisol (142). Corticosterone is less protective after subcutaneous injection than is cortisol, presumably because it is mobilized more rapidly from the site of deposition. (*d*) In rabbits, the protective effect is demonstrable primarily in large (2 to 4 kg.) animals; when smaller rabbits (0.5 to 1.0 kg.) are given cortisone and then endotoxin, bilateral renal cortical necrosis is produced. The cortisone, in the latter instances, acts as though it had supplanted the preparatory dose of endotoxin in eliciting the generalized Shwartzman phenomenon (6, 161, 166). (*e*) Dogs and guinea pigs are not protected against endotoxin by pretreatment with cortisone (167, 168, 169). (*f*) When cortisone or corticotropin is given for a prolonged period, the antipyretic effect of the hormones may be replaced by an exaggerated response to pyrogen (170, 171). (*g*) When cortisone is given to mice infected with organisms from which endotoxin can be extracted, the usual effect is to aggravate the infection, but with small doses of cortisone, and relatively avirulent organisms, some protection from the use of cortisone alone can be demonstrated (172). (*h*) The protective action of cortisone is not demonstrable in toxemias attributable to exotoxins from *Corynebacterium diphtheriae*, *Clostridium botulinum*, *Clostridium tetani*, *Clostridium perfringens*, and *Shigella dysenteriae* (172 to 177).

Thus, although the effect of corticosteroids on the lethal action of endotoxins is of great biologic interest, it is not demonstrable in all animal species and is not readily elicited unless the steroid has been given with or before endotoxin. Whether corticosteroids block the action of endotoxin in man, whether steroids will be effective after infection has supervened and endotoxin has been released, and whether the blocking effect on endotoxin will prove beneficial in clinical infection attributable to endotoxin-producing bacteria are problems that remain to be solved.

Potentiation of action of vasopressors.—Vascular collapse is one of the most serious complications of severe infection. The evidence that vasopressor agents such as norepinephrine are of value in the control of such collapse has already been cited. In addition, there is clear evidence that corticosteroids potentiate the pressor response to norepinephrine (178, 179, 180). The availability of clinically applicable methods for measuring norepinephrine and corticosteroid levels in the blood should help to determine whether, in

the presence of apparently adequate steroid levels, vasopressor activity can be potentiated by raising blood levels of corticosteroid still higher. At present, unfortunately, there are insufficient data to allow even conjecture.

With many new vasopressor agents reaching the market, the possible value of epinephrine should not be overlooked. Nakashima & Stoerck (181) have shown recently that epinephrine is more effective than cortisone in preventing vascular collapse in adrenalectomized rats given toxic chemicals or toxic electrolyte loads.

Summary

The balance between host resistance and microbial virulence can be shifted in one direction by large doses of adrenocortical steroids, and in the other by appropriate antimicrobial drugs. In addition there is evidence that the balance can also be influenced by other hormonal means such as somatotrophic hormone, norepinephrine, etc. The outcome is a consequence of the interplay of these factors, and since in most human infections host resistance is substantial, corticosteroids have been used in the management of infections with symptomatic relief and with relatively few reported adverse effects. However, these side effects, though not frequent, may be serious, and the effects of the hormones vary in different circumstances. Carefully controlled clinical studies will be required to determine whether the adrenocortical steroids offer any real advantage over other forms of symptomatic therapy.

Some evidence has accumulated suggesting that corticosteroids may, under proper circumstances, augment certain aspects of resistance to infection, but from the information now available, the clinical significance of these indications cannot be assessed.

Although the value of the corticosteroids in the management of infections, except when there is manifest adrenal insufficiency, is still uncertain, the attention focused on the mechanisms of host resistance and on the physiologic changes that occur during infection cannot help but add greatly to our understanding of disease.

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INFECTIOUS DISEASES[1,2]

(CONTROL OF INFECTION: BIOLOGICAL AND CHEMICAL MEANS OF PROPHYLAXIS)

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With the production of 2,400,000 pounds of antibiotics in the United States in 1955 (1) there is some justification for referring to the present as the "antibiotic era." As therapeutic agents, antibiotics have prevented millions of deaths from infection; as prophylactic agents, these drugs are being used increasingly to prevent the acquisition of infection. Yet chemoprophylaxis, however successful, probably will never equal the achievements of biological prophylaxis in preventing disease. The effectiveness of immunization procedures in altering specifically man's response to microorganisms or their products, along with man's capacity to control his environment, are the factors chiefly responsible for the increasing life span. The past year has seen a continuing effort to improve old vaccines and to develop new ones as better techniques or new infectious agents became available. Where disease can not be prevented by the resistance provided by immunization, attempts to control the host's microbial population by the administration of antimicrobial drugs sometimes have been rewarding but at other times have been harmful. No attempt has been made to cover all of the literature encompassed by the title of this review. Contributions to the general area of antibiotic or chemical prophylaxis and the use of antibiotics in certain specific situations have been discussed, but major attention has been devoted to recent studies on the preparation, administration, and evaluation of antibacterial and antiviral vaccines.

BIOLOGICAL PROPHYLAXIS

This section is concerned with contributions to active and passive immunization published since 1954. Excellent recent reviews by Edsall (2) and Love *et al.* (3) have dealt, respectively, with certain basic principles of immunization and the status of immunization in 1954. Currently accepted immunization schedules are tabulated in the paper by Love *et al.* (3) and are described in two recent booklets: *Report of the Committee on the Control of Infectious Disease* of the American Academy of Pediatrics[3] and the eighth edition of *Control of Communicable Diseases in Man* by the American

[1] The survey of literature pertaining to this review was completed in July, 1956.

[2] The following abbreviation is used in this chapter: BCG (Bacillus Calmette-Guérin).

[3] Evanston, Illinois (E. H. Christopherson, M.D.).

Public Health Association.[4] The Public Health Service's booklet *Immunization Information for International Travel*[5] is invaluable for physicians whose patients need prophylaxis based on the requirements listed therein. In a review of immunization procedures in the Armed Forces, Edsall (4) observed that the success of smallpox and yellow fever vaccination was attributable to "accident" and remarked that "all our efforts to date have not produced any other accidents so superbly successful as these two." Yet one could hardly expect more effective protection than that provided by the use of diphtheria and tetanus toxoids, to the study of which Edsall himself has contributed greatly. What is needed, as is true of some of the other immunizing agents to be discussed, is more effective application. Immunization can no longer be regarded as almost exclusively a pediatric procedure, for adults now can and should be assured of continued protection against certain diseases, particularly diphtheria and tetanus. It is hoped that needless and confusing variation in the immunization policies of the individual states in this country (5) will eventually be eliminated, and that standard routine schedules will be established for the immunization of adults as well as of children.

Combined Immunization

The use of multiple antigens in a single vaccine, as in diphtheria-tetanus-pertussis (DTP) triple vaccine, has long been an accepted procedure in the United States. British investigators, however, have only recently explored the use of combined prophylactic agents, and their studies have reopened the question of antigenic competition or interference (2, 6 to 11). Barr & Llewellyn-Jones (6) have summarized their evidence for the conclusion that the speed of the secondary response to the antigen to which there is pre-existing immunity, such as diphtheria toxoid, caused a "crowding out" of the immune response to tetanus toxoid. Parish (7) was concerned lest combined diphtheria-tetanus toxoid, when used as a booster dose for school children, produce considerable diphtheria antitoxin but little tetanus antitoxin if the children had already been immunized against diphtheria only. He advised using triple vaccine from the start, a practice shown (8) to produce satisfactory diphtheria and tetanus antitoxin titers in babies. The inclusion of pertussis organisms has an adjuvant effect (9, 10), increasing the potency of the vaccine. Thus, because injection of two fluid toxoids together results in some competition, the response to diphtheria antigen in a triple DTP vaccine is less than that obtained with a diphtheria-pertussis mixture, but greater than with diphtheria toxoid alone (11). Combined DTP vaccination of children has effectively reduced the incidence of the three diseases (12). In the case of diphtheria, elimination of the natural reservoir in children has removed cases and carriers as sources of natural immunization and left a susceptible adult population.

[4] 1790 Broadway, New York 19, N. Y.
[5] Government Printing Office, Washington 25, D. C.

Diphtheria

In Massachusetts, 55 per cent of all persons over 20 years of age have less than 0.01 unit of diphtheria antitoxin in their sera, and diphtheria has occurred in adults in recent years (13). The same is true of other areas (14, 15). Immunization of adults has previously required Schick testing and the cautious use of toxoid because the reaction rate to the usual dose of toxoid is high in adults. The earlier observations that small amounts of toxoid produce adequate antibody levels now have been extended, and an effective method of immunizing adults has been developed (13, 16). It was found that 1 Lf unit of toxoid (about 1/10 to 1/15 the standard pediatric dose) was the most that could be given an adult without causing undue reaction (4). Three doses of 1 Lf unit each produced solid immunity in 99 per cent of soldiers (16). This amount of diphtheria toxoid has been combined with 5 Lf units of tetanus toxoid and adopted for routine use by the Unted States Armed Forces (16) and the Massachusetts Department of Public Health (13). Edsall *et al.* (16) favor precipitated toxoids; Ipsen (13) prefers a fluid preparation without alum adjuvant. The vaccine may be used without prior Schick testing. It is administered to adults in two doses of 0.5 ml. each, one to two months apart, followed by a third injection one year later. This product is not used for primary immunization of children but can be used in children over six years of age who have already been immunized against diphtheria.

Tetanus

As he did with diphtheria toxoid (17), Greenberg assayed tetanus toxoids from a number of different countries and demonstrated great variation in potency (18), indicating the need for establishing international standards for both toxoids. The desirability of universal tetanus immunization for civilians (12, 19, 20) stimulated study of the duration of the protection provided by basic pediatric or military immunizations. Three similar studies of ex-servicemen have shown that a lapse of eight to ten years since the last preceding stimulus does not adversely influence a person's capacity to respond promptly and adequately to a booster dose of toxoid (21, 22, 23). Primary immunization should be followed by a booster dose in four to five years (for adults, use combined diphtheria-tetanus toxoids mentioned above). Subsequent boosters are recommended every four (23) to ten (21) years. Treatment recommended at the time of injury (19, 23) is as follows: (*a*) no certain history of immunization, give antitoxin; (*b*) patient fully immunized, give toxoid; (*c*) extensive injury with massive contamination and possibility of incubation period of two to six days, give antitoxin and toxoid simultaneously in different extremities.

Pertussis

The Whooping Cough Immunization Committee of the Medical Research Council of Great Britain is continuing to evaluate immunization against

pertussis (24). An initial study showed a fourfold reduction in the incidence of pertussis in the vaccinated groups, some vaccines being two to four times as effective as others. Studies now being made of vaccines prepared by different methods contemplate observing 30,000 to 40,000 children for a period of two years. Cashman (25) found antibody at birth in one-half of 76 infants tested; all but one had lost this passive antibody by the age of six months. Such data have led in the United States to administration of triple vaccine at two to three months of age.

Adenovirus Infections

The isolation of a new group of viruses and the identification of certain types within the group as etiologic agents of Acute Respiratory Disease (ARD) of military recruits, nonbacterial pharyngitis, pharyngoconjunctival fever, and keratoconjunctivitis (26), have permitted attempts to control these illnesses by active immunization.

The first of such studies was reported by Huebner *et al.* (27) who used a monovalent formaldehyde-inactivated and a heat-inactivated vaccine containing type 3 adenovirus. Type 3 virus has been related etiologically to a type of pharyngitis recently referred to as pharyngoconjunctival fever; when the virus is swabbed on the conjunctivas of susceptible volunteers, it produces a conjunctivitis and symptoms similar to those of pharyngoconjunctival fever (27). Forty-five persons having no neutralizing antibody at 1:8 dilution were given vaccine; 38 persons, with and without naturally acquired antibodies, comprised an unvaccinated control grup. Thirty-five of the 45 vaccinated persons developed postvaccination antibody titers of 1:8 or greater; 17 of the 38 nonvaccinees had naturally acquired antibodies. The volunteers were challenged by swabbing type 3 virus on the palpebral conjunctiva of one eye. Of 52 volunteers with prechallenge antibody, 14 (27 per cent) had definite illnesses; of 31 volunters without prechallenge antibody, 28 (90 per cent) had definite illnesses. Twenty (44 per cent) of the 45 vaccinated volunteers were not protected by the vaccines. The detailed data indicated that the vaccine-induced antibodies provided protection that was nearly equal to that afforded by naturally acquired antibodies.

An important problem for the military forces is the prevention of Acute Respiratory Disease (ARD) in recruits. Two types of adenovirus, type 4 and type 7, have been shown to cause ARD, and epidemiologically, this disease is followed by immunity, resistance being correlated with the presence of neutralizing antibodies. Hilleman *et al.* (28) evaluated the effectiveness of a formalin-killed vaccine containing types 4 and 7 virus. In 311 recruits, the vaccine produced a reduction in the incidence of respiratory illness beginning one week after the initial dose; 4.8 per cent of those given vaccine were hospitalized for respiratory illness compared with 23.8 per cent of a control group of 313 given placebo.

Adenovirus vaccines have been referred to by the lay press as "cold vaccines." All evidence has indicated that these agents are not etiologically

related to the common cold and can not be expected to protect against this disease.

Cholera

A series of papers on cholera studies by Pollitzer and co-authors (29 to 34) has appeared, the fourth of which deals with problems in the immunology of cholera (32), including immunity, toxin production, bacterial virulence, serological reactions, and antigenic structure. An extensive discussion considers natural, passive and active immunity, various means of vaccination, and evaluation of the immunity induced. Nine different methods of vaccine manufacture are reviewed, and reasons for inclusion of both the Inaba and Ogawa strains of cholera vibrio and for use of a two dose immunization system are given.

Pollitzer & Burrows (32) recommended the use of one dose of 1 ml. of cholera vaccine in countries like India where large scale immunization campaigns are required. The current vaccine approved by the Armed Forces consists of a suspension of 8,000 million organisms per ml. of the Inaba and Ogawa strains, preserved with phenol. The schedule calls for two injections of 0.5 ml., and 1 ml., 7 to 28 days apart, with booster injections every six months (3).

Influenza

Two reviewers (35, 36) of the immunological problems of influenza and the current status of the control of this disease through the use of heat-inactivated virus vaccines reached different conclusions after considering the problems posed by the appearance of new mutant strains. Since the A-prime strains appeared in 1947, the evolution of both A and B strains has resulted in a "continually emerging antigenic novelty" (35) which has often meant that antibodies stimulated by strains from previous years did not protect against the virus responsible for the current year's epidemic. This thesis is presented as an explanation for the poor protection afforded by the vaccine used by Davenport & Hennessy (37), for Lee virus induced low levels of antibody to 1954 and 1955 B strains.

Andrewes (35) considered the possibility of isolating new strains during precursor summer outbreaks of influenza, but pointed out that it is difficult to prepare a vaccine of known potency and on a large scale within a matter of months. He concluded that control of influenza by vaccination is doubtfully worth while on purely economic grounds since it would require vaccinating millions of people every other year.

Francis (36) summarized the vaccine experiments, conducted by the Commission on Influenza, which have demonstrated that a properly constituted vaccine is from 75 per cent to 95 per cent effective in the prevention of influenza, and suggested that broader use of such vaccine is desirable. He proposed that the problem of strain variation can be overcome by selecting strains of virus for the vaccine which contain significant quantities of the different antigenic components possessed by various strains. By pro-

viding adequate amounts of all the constituent antigens shared by influenza A viruses it should be possible to include in a vaccine all of the antigens of which a mutant A strain might be composed. As a result of antigenic variation, individuals in different age groups have different dominant antibody patterns, and vaccination should seek to stimulate antibody formation against antigens from strains which are not reflected in the naturally acquired antibody of a given age group. Since children are the most susceptible members of the population and have not yet developed a broad antibody spectrum, Francis postulated that they are the ones most in need of protection.

Glazier, Benenson & Wheeler (38) administered influenza vaccine to 614 infants and children between 1946 and 1953 and noted systemic reactions in 23 per cent. The incidence of reactions varied with the size of the dose per kg. but was not related to the allergic status of the family. There was no relation between the antibody response and the occurrence of a reaction. The use of vaccine at a naval base resulted in a high incidence of local reactions, but less than 0.5 per cent of those vaccinated had to be hospitalized because of systemic reactions. Of 200 officers, however, 13.5 per cent lost some time from duty because of reactions (39).

Emulsified oil adjuvant vaccines have given a greater and more sustained antibody response than saline vaccines, but a decrease in antibody levels was noted one year after inoculation (40). There was no increased breadth in antibody response to heterologous virus, and it was concluded that the use of adjuvants is not the solution to the problem of immunological specificity. Composition of a vaccine to give the antigenic coverage desired by Francis has not been accomplished; the immunity produced is short lived; reactions, although rarely serious, carry part of the inconvenience of the disease. Until the effectiveness of "properly constituted" vaccines has been demonstrated over a period of years, influenza vaccine is not recommended for general or pediatric use; it may be desirable for special groups such as military forces, hospital staffs, or patients for whom influenza carries greater risk.

Plague

Just as sanitation is the key to the control of typhoid fever, so is eradication of rodents the fundamental measure in the prevention of plague. Attempts to produce more effective vaccines continue, although it is realized that immunity after recovery from a natural plague infection is relative. Active immunization with a vaccine of killed bacteria confers some protection, and the Armed Forces have used formalin-killed suspensions of *Pasteurella pestis* given as two subcutaneous injections at seven to ten day intervals, followed by booster doses every four months (3).

Ehrenkrantz & Meyer (41) tested three preparations for their ability to protect primates against pneumonic plague: (*a*) living, avirulent *P. pestis*, strain E. V. 76; (*b*) formalin-killed virulent organisms, strain Yreka; and (*c*) Fraction I, a soluble antigen extracted from the plague bacillus.

Little protection was provided by the dosages and schedules recommended for antiplague immunization of man. Further, massive vaccine doses given over a short period of time showed little increase in the survival rate. Survival was increased by extending the interval during which vaccination took place to 45 to 170 days, the length of this interval being more important than the total dose of vaccine given. Four monkeys given 55 mg. of Fraction I over 170 days were completely protected from intratracheal instillation of 10,000 virulent organisms. In general, resistance was associated with measurable serum antibodies at the time of challenge. Removal of antibodies to Fraction I from antifraction I serum caused complete loss of the protective power of that serum. It was concluded that an effective antiplague vaccine must contain an adequate amount of Fraction I antigen, and that immunization should be spaced over long intervals and be reinforced by subsequent booster injections (41).

Poliomyelitis

Active immunization.—The development and application of a vaccine for poliomyelitis has been so extensively described, discussed, and debated in the past year that it is impossible, and, indeed, unnecessary, to review all of the contributions in this field. In a series of papers published in August, 1955, Salk (42), Scheele & Shannon (43), Dublin (44), Francis (45), and Scheele (46) reviewed data regarding the preparation of the formalin-inactivated virus vaccine and determination of its effectiveness in preventing paralytic poliomyelitis. Bodian (47), Francis (48), and Salk (49) have discussed the dynamics of immunity in relation to the control of poliomyelitis by immunologic methods. Digests of vaccine information, edited by Van Riper (50), have been distributed to all physicians by the National Foundation for Infantile Paralysis. Van Riper has stated that "the goal of control of paralytic poliomyelitis is now clearly in sight" (51), and the Foundation has been represented (52) as now presenting "the problem of prevention as one of logistics and not one of medical science, with the inference that final accomplishment of the end so devoutly to be wished for is now a matter of vaccine production, unrelated to further research."

Research reported in the past year will be reviewed here under three headings: (*a*) antigenicity of Salk vaccine, (*b*) effectiveness of killed-virus vaccine, and (*c*) immunization with attenuated living virus.

Antigenicity.—Salk (49) has stated that man reacts to poliomyelitis antigen in accordance with the same laws that govern his reaction to other antigens and has presented data (42, 49) indicating that antibody induced with formalinized vaccine persists more than two years and that the effects of primary immunization are such that revaccination—a booster dose as long as two years later—results in sharp rises of antibody. Brown & Smith (53) studied the antibody response of 135 infants and 116 preschool children. In 92 children given three injections of vaccine at monthly intervals, the majority, including those six months of age and under, responded with in-

creased neutralizing antibodies to all three types of virus. In another group of 40 children who received two injections for primary vaccination, the titers were not as high as in a group receiving three inoculations. Of 13 infants given one inoculation, only a few developed low level antibodies, although reinoculation later resulted in definite increases in antibody. The authors (53) concluded that secondary inoculation with a good vaccine provoked as good a response in infants as in children even when the primary dose was apparently ineffective and suggested that even a "poor" vaccine may "condition" recipients to subsequent stimulation.

It is recommended that two 1 ml. injections two to six weeks apart be given for primary immunization, and that a third dose be given six to twelve months later. How long antibodies so induced will last is unknown; whether persistence of immunity is dependent on the continued presence of such antibodies is being debated. It is Salk's (49) contention that individuals "conditioned" by vaccination, even though circulating antibodies have disappeared, may develop a hyperreactive immunologic state in which virus multiplying at the primary site of infection could stimulate antibody production fast enough to prevent viremia and invasion of the central nervous system. On the basis of this concept, Salk challenged the assumption that only a live-virus vaccine will produce the necessary changes required for lifelong immunity.

Effectiveness.—Data regarding the effectiveness of Salk vaccine in 1955, a year when most of those vaccinated received only one dose, have been summarized by Van Riper (50, 51). Langmuir (54) reported the findings of studies conducted by 22 states and New York City involving over eight and a half million children as follows: among vaccinated children the attack rate was 6.3 per 100,000; among the unvaccinated, the attack rate was 29.2 per 100,000. Thus, there was a reduction of 78 per cent in the rate of paralytic poliomyelitis among vaccinated children. Paralytic admission rates in 1955, as compared to 1954, dropped 56 per cent in eight year olds and 51 per cent in seven year olds, the vaccinated age groups, in contrast to a 23 per cent decline for the total population (50). Data from a severe type 1 epidemic in Massachusetts confirmed the 1954 field trials. Pope *et al.* (55) reported 130 cases among 137,968 children who received one dose of vaccine, an attack rate of 94.5 per 100,000. Fifteen cases occurred among 22,673 who received two or more doses, a rate of 56.4 per 100,000. Among 278,532 unvaccinated children there were 553 cases, a rate of 198.2 per 100,000. The effectiveness of the vaccine for all cases was 53 per cent; for paralytic cases, 60 per cent. The severity of the Massachusetts epidemic is apparent when these data are compared with those for Canada in 1955 (50, 51). Among children who received two of more doses of vaccine, the paralytic rate was 0.84 per 100,000; among unvaccinated children the rate was 5.76 per 100,000. The Canadian figures indicate an effectiveness of about 85 per cent. On the basis of such data the hope has been expressed that the vaccine will be 80 per cent effective in the age groups inoculated in 1956 and will reduce the total incidence of paralytic poliomyelitis by 51 per cent (50).

Live-virus vaccines.—Wenner (56) and Lepine (57) reviewed the use of attenuated virus vaccines, and Lepine has recommended primary vaccination with killed vaccine followed by revaccination with attenuated virus as the best method of immunization. Since natural infection provides lifelong immunity, Sabin (58) and Koprowski *et al.* (59, 60) have sought to duplicate the natural process of immunization by feeding avirulent, or nonparalytogenic, living virus. Koprowski (59) has defined the characteristics of a living agent which determine its acceptance as a vaccine as follows:

> 1) inability of the virus to produce serious illness in the vaccinated host; 2) nontransmissibility of the virus from an "infected" to a non-infected host; or, if transmission occurs, fixation of the modified properties; 3) presence of sufficient amount of living virus in a final product to meet minimum titer requirements; 4) evidence of adequate antigenicity following a single administration of the virus.

Koprowski *et al.* (60) have reviewed their total experience in immunizing children with living virus. The strains used were attenuated by animal passage. The first strain tested (in 1950), the TN strain, is a rodent-adapted type 2 virus which is not pathogenic when injected intracerebrally in monkeys. Administered intraspinally in high doses, it causes paralysis in an occasional monkey. The TN strain is also noncytopathogenic for tissue culture cells. Type 1 was represented by the SM strain, also a rodent-adapted virus, which is maintained by alternate passages in chick embryo tissue cultures and in monkey kidney cultures. The SM strain is similar to the TN strain on intracerebral and intraspinal injection of monkeys; it differs from the TN strain in that it is cytopathogenic for monkey kidney epithelium. Altogether, 150 nonimmune subjects have been given the TN (type 2) strain and 75 the SM (type 1) strain; none suffered any ill effects. When the viruses were administered simultaneously, the type 1 virus alone produced antibodies. This interference was overcome by giving type 2 virus first or in larger amounts. With the exception of those exhibiting interference, all subjects fed either of the viruses developed homotypic antibodies. The subjects excreted the noncytopathogenic TN virus only sporadically, whereas the SM virus was recovered from every individual who ingested it. Under the conditions of the isolation unit, transmission of the SM strain occurred to 5 of 15 contacts. The rate of alimentary infection and the development of antibody was not influenced by the simultaneous administration of immune globulin.

Sabin (58) used tissue culture techniques to segregate avirulent variants from virulent strains of each of the three immunologic types of virus. His variant strains were avirulent for monkeys by the intracerebral, oral, and parenteral route, but, like the TN and SM strains, produced paralysis after intraspinal injection of monkeys. Inoculation of these viruses [derived from Mahoney (type 1), YSK (type 2), and Leon (type 3) strains] into the spinal cord of chimpanzees did not produce paralysis, yet feeding of the strains induced immunogenic alimentary infection in chimpanzees. Adult volunteers were found to be more susceptible than chimpanzees to infection

by the oral route. Whether or not the vaccine localized and multiplied in the throat depended on the size of the dose swallowed, and the antibody response was greatest in the volunteer who had the most multiplication of virus in the throat. Despite extensive multiplication of virus in the alimentary tract, none was detected in the blood.

The reversion of avirulent strains to virulent ones after human passage is a possibility that has challenged those interested in live polio virus vaccines just as it did those concerned with yellow fever, rabies, and BCG. It has been pointed out (47) that those concerned in developing avirulent strains for vaccination have not yet produced evidence for the safety and adequate potency of such vaccines produced on a large scale. The same, it should be added, was at one time true of Salk-type, formalin-killed vaccines. It is doubtful, however, that large scale field trials of any new poliomyelitis vaccine will ever again be possible in this country.

Passive immunization.—Passive immunization against poliomyelitis has been reviewed by Hammon (61), and there is little to add to the data presented by T. F. McNair Scott in the *Annual Review of Medicine* for 1955. Opton, Nagaki & Melnick (62) examined 65 samples of gamma globulin by tissue culture neutralization tests. Each sample, regardless of origin, contained type-specific antibodies for all three types, and more than 90 per cent of the titers lay in the range between 1:400 and 1:2000. Brown, Rabson & Schieble (63) demonstrated that most subclinical infections, if present at the time of gamma globulin inoculation, were not eliminated, and that active immunization by subclinical infection was not inhibited by gamma globulin. To explore the feasibility of using a combination of gamma globulin and vaccine for passive-active immunization under circumstances requiring rapid protection, Brown, Rabson & Craig (64) administered Salk vaccine to 27 children three days after the injection of a dose of gamma globulin twice that usually administered to human beings. Antibody titers so induced were adequate and comparable to those obtained in tuberculous children given injections of the same lot of vaccine. It would seem logical, therefore, to use both gamma globulin and vaccine in the face of an explosive epidemic of poliomyelitis.

Rabies

The present status of protection of man against rabies has been reviewed by Meyer (65) and Hodes (66); Love *et al.* (3), as did Hodes, included tables giving the indications for rabies prophylaxis. Meyer (65) has pointed out that traditional control measures, such as elimination of stray dogs, often prove inadequate and difficult to enforce, and that only with the adjunct of canine mass vaccination can the principal source of human rabies be eradicated. Progress made in the active immunization of dogs and man and in the passive immunization of man is reviewed here.

Active immunization.—The development of the Flury strain of chick embryo-adapted rabies virus by Koprowski *et al.* (67, 68) is a significant

advance in the control of rabies. Koprowski (67) has recounted how the Flury strain was isolated from the brain of a young girl of that name by Dr. Harold Johnson in 1939 by intracerebral inoculation of day-old chicks. After 138 chick-brain passages, the virus was adapted to the chick embryo, and thus represents a strain of virus that has been maintained in non-mammalian hosts. Around the one-hundred and eightieth egg passage, the virus lost its pathogenicity when injected into the brain of adult mice, rabbits, and dogs. This change in pathogenicity was reproducible, and permanent, for the virus has shown no tendency to regain its virulence or ability to be transmitted following vaccination of more than three million dogs (66). Intramuscular injection of this attenuated virus stimulated the production of neutralizing antibodies in dogs, calves, and chimpanzees sufficient to protect against challenge with virulent street viruses (67). Johnson (69) has shown that immunity produced with the Flury strain live-virus vaccine is superior to, and of longer duration than, that obtained with phenolized brain-tissue vaccine. The chick-embryo vaccine has been tested successfully in the field where it was a decisive factor in controlling rabies in dogs (70).

It may well be more difficult to obtain public acceptance of the vaccine for the protection of its dogs and its citizens than it was to develop the vaccine. Two papers considered this problem as related to rabies control in Detroit (71) and Denver (72). Anderson & Cameron (72) have described Denver's approach to control in which licensing of dogs was discontinued to eliminate the idea that the control of rabies was connected with taxation. The success of Denver's program was attributed to acceptance of the dog immunization by an informed and educated public and to the active participation of the practicing veterinarians.

Until rabies is eradicated physicians will be faced with the management of dog bites by the administration of rabies vaccine to humans. Cook and co-workers (73) reported on the use of phenolized rabies vaccine in Texas from 1939 through 1953. During that time there were 42 human deaths from rabies. Sixteen cases of postvaccinal paralysis with one death occurred among 8,430 persons given vaccine, a severe reaction rate of about 1 in 500. A striking observation was that 66 per cent of those vaccinated were actually bitten by a laboratory-confirmed rabid dog.

The hope has been expressed that the avianized Flury vaccine may be also used for man and thus eliminate the danger of reactions to the nervous tissue in current human vaccines. Schwab *et al.* (74) administered Flury virus intramuscularly to 98 volunteers. Single doses of 4 to 8 gm. produced detectable antibody in only 43 to 64 per cent of volunteers. In contrast, all of nine individuals given conventional Pasteur treatment had a strong antibody response by the fifteenth day. All but one of 14 persons given a total of 12 gm. of embryo material and all of six given 20 gm. (in three to ten doses) responded with detectable levels of neutralizing antibody. Even with the largest doses, however, the average antibody levels were not equal to those observed in the control group receiving attenuated fixed virus in

rabbit brain suspension. Schwab *et al.* (74) concluded that Flury virus, at the passage level employed, is capable of little or no multiplication in man. They pointed out that the level of antibody necessary to protect man is unknown and expressed the hope that purification will produce a more effective vaccine.

Passive immunization.—Koprowski *et al.* (67, 75, 76) have shown that administration of hyperimmune antirabies serum protects animals against experimental rabies and does not interfere with the immunizing capacity of Flury egg vaccine. In animals, hyperimmune serum gave more protection than vaccine alone, and the combination of the two gave best results. Antiserum did not reduce the mortality if given more than 72 hr. after exposure. When used alone, even though it did not prevent death, immune serum prolonged the incubation period. Habel considered that this effect had important therapeutic implications since the majority of vaccine failures in humans occur in cases with short incubation periods (77). An opportunity to test hyperimmune serum in humans was provided when a rabid wolf bit 29 persons in an Iranian village within a few hours (78, 79). Eighteen persons suffered severe head wounds. Five of them were given two injections of serum on the first and fifth days and phenolized vaccine for 21 days; all survived. Seven others received one injection of serum and a 21-day course of vaccine; one died. Five patients received vaccine only; three died. A child whose dura mater had been torn by the bite was given six serum injections and vaccine; he survived. The mortality rate of those given vaccine alone was the same observed over the previous 15 years, when approximately 40 per cent of persons bitten on the head by rabid wolves had died (78). These dramatic results demonstrated that antibody early in and throughout the treatment period, obtained by the combined use of hyperimmune serum and vaccine, was more effective in preventing rabies after severe exposure than was vaccine alone (79).

Since rabies virus may persist at the wound site for as long as three days, antiserum should be infiltrated in and around the wounds. Further, because the serum does not inhibit an active response to the vaccine, it may be given at the time of a bite and if the animal is subsequently found to be rabid, vaccine may be started up to a week later. The dose of the hyperimmune serum, prepared in horses and requiring all the usual precautions, is 0.5 ml. per kg.

Smallpox

Use of live vaccinia virus for immunization against smallpox is an effective and established procedure, but there are still areas of the world where protection of the population by vaccination has not been accomplished. One reason for this failure is the absolute requirement that the virus in the vaccine must be alive and the fact that glycerinated lymph deteriorates rapidly at temperatures above 0°C. Thus vaccination campaigns in remote areas and hot climates have been hampered by the need for storing vaccine

in the frozen state. Current advances have been related to this problem.

Collier (80) reviewed the work that has been done on preservation of vaccinia virus and reported (81) the development of a stable vaccine. Attempts have been made to preserve virus by: (*a*) the addition of protective substances, (*b*) by drying from a liquid state, and (*c*) by drying from a frozen state. Collier (81) started with partially purified sheep virus and found that 5 per cent peptone protected the virus during freeze-drying and during storage at 45°C. After storage for one year at 22°C, the egg titer of such freeze-dried vaccine fell from $10^{-7.28}$ to $10^{-6.04}$, or by a factor of 17. After four months at 37°C., the titer fell from $10^{-7.28}$ to $10^{-6.28}$, only a tenfold decrease. This demonstrated stability was verified when the virus gave a full quota of successful primary vaccinations of children after the above temperatures and times of storage.

In reviewing the use of smallpox vaccine, McClean (82) cited the following developments made in the last 30 years: (*a*) improved methods of destroying bacteria, (*b*) methods of reducing amount of extraneous tissue debris, (*c*) cultivation of virus in embryonated eggs and tissue culture, (*d*) production of stable dried vaccines, particularly the development of drying from the frozen state, and (*e*) improvement in methods of titrating potency. A trial to test further the stability of Collier's Lister Institute vaccine is being conducted by the World Health Organization. If the effectiveness of the freeze-dried vaccine is confirmed, it should find wide application, not only in areas with inadequate refrigeration, but throughout the world.

Tuberculosis

Many contributions were made in the past 18 months to the voluminous literature on the controversial subject of active immunization for the prevention and control of tuberculosis. Among those reviewing BCG vaccination were Drolet & Lowell (83), Irvine (84), and Seagle (85). A volume (86) on mass BCG vaccination campaigns from 1948 to 1951 presented statistical reports on 17 such campaigns in which 30 million persons were tuberculin-tested and 14 million were vaccinated. No conclusions regarding effectiveness were possible, but the data are useful as a record of the level of tuberculin sensitivity in various parts of the world.

Palmer and his associates (87) in the Tuberculosis Program of the Public Health Service have outlined some basic experimental studies on vaccination, allergy, and immunity in tuberculosis. Studies on the effect of varying the dose of BCG showed that as the dose of living BCG was increased, groups of guinea pigs showed a progressive increase in the degree of post-vaccinal tuberculin allergy, in the size of the vaccinal lesion, and in length of survival after challenge with virulent organisms. Heat-killed BCG resulted in weak allergy and a short survival time. The data were interpreted as implying a possible advantage in the induction of a high degree of tuberculin allergy (88).

The heat-killed bacilli provoked vaccinal lesions about as large as would

be expected from a corresponding dose of living BCG, findings which were in agreement with results in man. Persons vaccinated with heat-killed BCG have a very low degree of postvaccinal allergy, yet the size of the vaccinal lesion differs slightly from that induced by living BCG. Palmer *et al.* (89) suggested, therefore, that the combination of a large vaccinal lesion and a low degree of postvaccinal allergy should invite suspicion that the vaccine contained mainly killed bacteria, and, perhaps, the presumption that it produced only a low degree of immunity.

Since morbidity from meningitis and miliary tuberculosis is highest in the first three years of life, attention has been focused on this critical period. Gaisford (90) reported that vaccination at birth is safe and effective. He obtained the quickest conversions with standard Danish BCG and found half-strength vaccine preferable for infants. Over a five year period, 5216 newborn infants, about 40 per cent of those offered vaccination, were vaccinated and checked annually. In Manchester, from 1949 to 1954, there were 50 deaths from tuberculosis in children under five years of age and 12 deaths in infants less than one year old. There were no deaths in vaccinated children, although 537 had known contact with the disease. Twenty-eight mothers developed clinical tuberculosis at some time after their infants were vaccinated; none of the infants developed tuberculosis.

Another critical age given attention was adolescence. For the first controlled trial of BCG in Great Britain, the Tuberculosis Vaccine Clinical Trials Committee (91) elected to study a narrow and susceptible age group, 14 to 15 years, under the ordinary conditions of urban and suburban life prevailing in an industrial community. More than 56,700 children in their final year at schools in or near North London, Birmingham, and Manchester were included in the tests. Forty per cent, 22,600, were tuberculin-positive on entry into the study. Those giving a negative reaction were divided by a random process into three groups: 13,300 were not vaccinated; 14,100 were given BCG; 6,700 were given Vole bacillus (*Mycobacterium muris*) vaccine. The success of follow-up was the same in all groups. Data on all definite and suspected cases of tuberculosis were reviewed by an assessor without knowledge of the vaccination status of the participant. Within two and one-half years of entry to the trial, there were 84 cases in the three groups. The annual incidence rates for concurrent groups were: (*a*) unvaccinated controls, 1.94 cases per 1000; BCG vaccine, 0.37 per 1000; (*b*) unvaccinated controls, 2.06 per 1000; Vole vaccine, 0.44 per 1000. Each vaccine, then, conferred a substantial and similar degree of protection against tuberculosis over a two and one-half year period. Continued observation has disclosed no evidence of any diminution in the efficacy of either vaccine up to four years. The Committee estimated that vaccination prevented one case of tuberculosis annually for every 1000 children given tuberculin tests prior to vaccination. Meningitis or miliary spread, or both, occurred in 6 of 64 cases of tuberculosis in the unvaccinated group; such spread did not occur in the 20 cases in the vaccinated groups. Complications of vaccination noted were occasional

regional adenitis, delayed healing of local lesions, and two cases of erythema nodosum. A number of children given Vole bacillus vaccine developed lesions indistinguishable from lupus vulgaris.

Enell (92) has published a detailed account of BCG vaccination, tuberculin allergy and tuberculosis in Stockholm's school children. His survey described how BCG was introduced into Sweden in 1920 and how Scandinavia became a leader in BCG vaccination. Enell has tabulated the details of 27 vaccination studies reported from 1932 to 1953, the last column of the table showing the per cent protection of those vaccinated. In terms of morbidity, effectiveness of BCG ranged from 57 to 97 per cent protection; in terms of mortality, effectiveness ranged from 58 to 100 per cent protection. Enell then described the program for the voluntary vaccination of school children, noting that those refusing vaccination were found in all classes in equal proportion and that tuberculosis was no longer a disease of the poor in Stockholm. Of 843 nonvaccinated children, there were 388 spontaneous tuberculin converters, and 46 per cent of these had clinical tuberculosis. Of 3112 vaccinated children, 7 developed tuberculosis. There were no deaths in either group. Comparing children who were tuberculin-negative and unvaccinated on starting school, Enell calculated that BCG afforded 98 per cent protection. At the end of nine years, 91.6 per cent of the children were still tuberculin-positive, indicating a reversion rate of 1 per cent per year. The following vaccination program was recommended: BCG shortly after birth with tuberculin testing and revaccination at ages 7 (school), 15 (end of school), and 20 (military conscript), and every seventh year thereafter.

The three reports summarized above have presented additional evidence in support of the effectiveness of BCG vaccine, and one (92) has outlined a program for mass immunization in Sweden. Effective or not, however, the value of BCG vaccination in the total approach to the control of tuberculosis, particularly in the United States, continues to be seriously questioned (83), and even the vaccine's most ardent supporters in Scandinavia (93, 94) are debating the justification of mass vaccination. One of the most interesting publications to appear regarding BCG was the account[6] of a Scandinavian Symposium (94) on the subject of mass vaccination. Participants were: Wallgren, Törnell and Sievers from Sweden; Groth-Petersen, Denmark; Gedde-Dahl and Heimbeck, Norway; Savonen, Finland; and Palmer, United States. In his introduction, Wallgren emphasized the extent to which the tuberculosis situation has changed since 1927, examined what BCG vaccination can be expected to achieve, and concluded that BCG should protect against the effect of primary infection and its immediate sequelae, such as meningitis, but was of doubtful value in protecting against late postprimary pulmonary tuberculosis. Wallgren (94) still believed that general BCG vac-

[6] An English translation is available on request to the Publication Services, Tuberculosis Program, Division of Special Health Services, Public Health Service, Washington 25, D. C.

cination should be used in countries where primary infection occurs in early childhood but has now decided that mass vaccination is unnecessary in countries like Sweden where primary infection occurs late, and there is satisfactory natural resistance. He therefore recommended the gradual discontinuation of the vaccination of school children and then of newborns while continuing vaccination of children leaving school and of military conscripts.

Groth-Petersen (94) began his discussion as follows.

> It is surprising and remarkable that Wallgren, who has been one of the great pioneers of the use of BCG vaccination in the fight against tuberculosis, should advocate gradual winding up of mass vaccination at a time when, in my opinion, it is only now that we may begin to reap the fruits of mass vaccination.

Groth-Petersen then gave his reasons why physicians in Denmark will endeavor to vaccinate systematically all young people for years to come. The data discussed and the arguments advanced by Groth-Petersen and others cannot be reviewed here, but the comments of Palmer (94) are presented as representing the view of many in the United States, where, in 1954, only 4.6 per cent of Navy recruits were tuberculin-positive (93).

> The present situation in the United States without BCG so closely parallels that in Scandinavia with BCG, we would be wise not to start what Sweden now proposes to discontinue. . . . There is no compelling reason to believe that we have done less well in controlling tuberculosis without BCG than countries where BCG has been widely used. . . . By deliberately not using BCG we are still able to assume that a positive tuberculin reaction indicates infection with virulent tubercle bacilli. We can still measure our infection rates, locate sources of infection, and more efficiently diagnose cases in need of treatment. And, what may be still more important for the future, we can identify, keep under observation, and perhaps even treat prophylactically, positive tuberculin reactors who now seem to be those at greatest risk of developing clinical tuberculosis.

Typhoid Fever

Use of triple vaccine for immunization against typhoid and paratyphoid fevers has long been an accepted procedure, although, as pointed out by Edsall (4), there is yet to be a critically controlled study of the effectiveness of the vaccine. Edsall (4) has tabulated some of the situations which appeared to provide evidence of the value of the vaccine, and the experience of the United States Armed Forces in Korea has been cited (3) as speaking for the effectiveness of immunization. Doubt has been cast on the value of triple vaccine because of the occurrence of two outbreaks of typhoid fever in immunized British airmen (95) with second attacks of typhoid in some (96).

Edsall (4) has produced an experimental infection in chimpanzees which closely resembles disease in man and plans to use this primate to evaluate the effectiveness of current vaccine and of vaccines containing isolated and purified antigens. He has presented preliminary data showing that vaccina-

tion protected all of ten animals from a challenge that induced bacteremia in five of seven control animals. Additional data should soon be available regarding field trials of typhoid vaccine in Yugoslavia.

CHEMICAL PROPHYLAXIS

The effectiveness of antimicrobial drugs as therapeutic agents naturally led to their use as prophylactic agents on the assumption that a drug which can eliminate an organism after it has initiated an infection should be able to prevent the organism from ever becoming established. When chemoprophylaxis has been directed against certain specific organisms, such as gonococci, meningococci, and β-hemolytic streptococci, the assumption has proved to be valid. When chemoprophylaxis has been directed against bacteria in general in an effort to provide "blanket" protection, an expansion of the assumption which would require drugs that are effective against all pathogens, the success achieved has been variable. Since antibiotics used for prophylactic purposes may induce complications (97) and increase the frequency with which antibiotic-resistant bacteria emerge (98 to 101), the use of such agents can be justified only on the basis of proved effectiveness.

Weinstein (102) classified the purposes for which chemoprophylaxis has been used as follows:

> 1) to protect healthy individuals, either singly or in groups, against invasion by specific organisms, 2) to prevent secondary bacterial infection in people acutely ill with diseases for which the antimicrobial agents are not effective, 3) to reduce the risk of infection in patients with various types of chronic illness, and 4) to inhibit the spread of disease from areas of localized infection, or to prevent infection in general, in persons who have been subjected to accidental or surgical trauma.

The first purpose relates to "specific" protection, the other three to "general" protection. The data reviewed here are considered under these two headings.

Prevention of Infection with Specific Organisms

Rheumatic fever.—The relation of Group A β-hemolytic streptococci to the occurrence and recurrence of attacks of rheumatic fever is now generally accepted (103), as is the efficacy of penicillin in treatment of streptococcal infections and eradication of the infecting bacteria. The problem of prevention and control of rheumatic fever, and hence of rheumatic heart disease, thus resolves itself into two aspects: (*a*) prevention of the first attack of rheumatic fever, and (*b*) prevention of recurrences or recrudescences.

The present approach to prevention of the first attack of rheumatic fever has been discussed by Hubbard (104). This approach is based on the observations that rheumatic fever develops in approximately 3 per cent of patients with untreated streptococcal infections and that effective antibiotic treatment of the preceding streptococcal infection results in a marked reduction in the incidence of this complication. Eradication of the infecting streptococci is apparently the essential factor, since treatment with penicillin is most effective both in eliminating the bacteria and in reducing the incidence

of rheumatic fever. The broad-spectrum antibiotics are only moderately effective in both respects (105). Sulfonamide drugs, which do not eliminate the bacteria, likewise do not affect the occurrence of the complication (106). On this basis, the Committee on Prevention of Rheumatic Fever and Bacterial Endocarditis of the American Heart Association has recommended the following treatment schedules for streptococcal infections (107). (*a*) Intramuscular penicillin—one or the other of the following: (i) Benzathine penicillin G: children, 1 intramuscular injection of 600,000 units; adults, 1 intramuscular injection of 600,000 to 900,000 units; (ii) Procaine penicillin with aluminum monostearate in oil: children, 1 intramuscular injection of 300,000 units every third day for 3 doses; adults, 1 intramuscular injection of 600,000 units every third day for three doses. (*b*) Oral penicillin: Children and adults, 250,000 units three times a day for a full 10 days.

The Committee emphasized that treatment must be continued for the entire 10 days, even though the patient is asymptomatic, if rheumatic fever is to be prevented by eradication of the streptococci. For this reason, many investigators and clinicians, such as Breese & Disney (108) and Mohler *et al.* (109, 110), have preferred injectable penicillin to oral preparations, particularly in view of the failure of many patients to take penicillin by mouth as prescribed (109).

Adequate treatment of the preceding streptococcal infection, however, is not the sole solution to the problem of preventing rheumatic fever. Rammelkamp *et al.* (111) have estimated that approximately 40 per cent of patients admitted to a military hospital for rheumatic fever were not seen or treated during the preceding streptococcal infection either because of mildness of the infection or failure to make a correct diagnosis. Breese & Disney (112) had an accuracy of 75 per cent in clinical diagnoses when checked against bacteriological cultures, although the combination of clinical features and cultures gave greater accuracy. For these reasons, attempts have been made to prevent the streptococcal infection itself. Denny (113) has reviewed the several studies which have been made along these lines, employing either the sulfonamide drugs or penicillin. Both drugs have been shown to control outbreaks in closed population groups, such as military organizations and institutions, or in families, although penicillin is considered to be preferable. Practical application of mass chemoprophylaxis in the general population, however, does not now seem feasible. Community programs are now being attempted (114) for the control of rheumatic fever, based on early detection and adequate therapy of streptococcal infections.

Not all investigators accept the thesis that adequate penicillin therapy of streptococcal infections will prevent the subsequent development of rheumatic heart disease. Weinstein, Boyer & Goldfield (115) have reported the results of a seven year follow-up study of 110 of 167 patients treated for scarlet fever with adequate doses of penicillin. Of the 167 patients, 126 were less than 10 years of age at the time of the streptococcal infection. Acute rheumatic fever was diagnosed in 12 of the 167 patients, primarily on

the basis of appearance of prolongation of atrioventricular conduction after a latent period. Only two of the cases fulfilled Jones' criteria for the diagnosis of rheumatic fever. At the time of followup, the 110 available patients included 10 from the group of 12 previously diagnosed as having developed acute rheumatic fever seven years earlier. In six of these patients, valvular lesions of mitral stenosis and insufficiency were present; two also had evidence of aortic lesions. Two patients had evidence of "probable rheumatic heart disease," and two had no signs of cardiac involvement. None of the remaining 100 patients had evidence of heart disease. The authors suggested that penicillin therapy of streptococcal infection in children may suppress the characteristic features of rheumatic fever except the electrocardiographic changes, but "may not significantly decrease the occurrence of acute rheumatic carditis." These results are difficult to evaluate since the study was not controlled, only historical data were available regarding intervening infections, and 57, or 34 per cent, of the original group were lost from the study. They do indicate, however, that further investigations of this type are needed.

The prevention of recurrences in patients who have experienced their first attacks of rheumatic fever presents a somewhat different problem. Here the patients should be protected, if possible, from any further contact with β-hemolytic streptococci, since the risk of another attack of rheumatic fever and further cardiac damage is much greater, presumably because these patients automatically constitute a highly susceptible group by virtue of their previous attack. From 20 to 80 per cent of such patients will develop another attack of rheumatic fever following a streptococcal infection. Prevention therefore depends on continuous prophylaxis rather than solely on treatment of the acute streptococcal infection (107).

Ample evidence has accumulated during the past 15 years to show that the sulfonamide drugs are effective in the prophylaxis of streptococcal infections in rheumatic subjects (113). Penicillin, administered either orally or parenterally, has also proved to be effective prophylactically (113). Most of the recently reported studies have been concerned with the use of benzathine penicillin which, administered parenterally, will apparently prevent acquisition of streptococci for a period of approximately 1 month. Thus Chancey *et al.* (116) showed that a single intramuscular injection of either 600,000 units or 1,200,000 units of benzathine penicillin in young adults was effective in eradicating the carrier state and preventing or reducing acquisitions of β-streptococci over a three-week period. The larger dose of 1,200,000 units of benzathine penicillin was more effective in these respects than was the dose of 600,000 units, or oral penicillin in doses of 250,000 units twice daily for 10 days. The latter two schedules gave similar results. Stollerman, Rusoff & Hirschfeld (117) administered monthly injections of a single dose of 1,200,000 units of benzathine penicillin to out-patients and in-patients with rheumatic fever at Irvington House. Adequate control populations were not available. During a two year period there were no recurrences of rheu-

matic fever among the 145 out-patients who presumably had much greater exposure to hemolytic streptococci than did the in-patients. Four of the in-patients had laboratory evidence of infection, but only one had clinically apparent streptococcal pharyngitis. Cardiac involvement progressed in three patients who had evidence of carditis at the beginning of the study. In one of the remainder cardiac lesions did develop. It should be noted that two patients, one an out-patient and the other an in-patient, developed subacute bacterial endocarditis caused by *Streptococcus viridans* while on this prophylactic regime. Both were cured by treatment with large doses of crystalline penicillin G.

Oral administration of benzathine penicillin G has also been employed for the prevention of streptococcal infections and recurrences of rheumatic fever. In a comparison of this procedure, namely, administration of one 200,000-unit tablet daily, with daily oral administration of 0.5 to 1.0 gm, of a triple sulfonamide preparation, Markovitz & Hemphill (118) concluded that the two regimes were of approximately equal effectiveness.

Benzathine penicillin G has certain attractive advantages for prophylaxis of streptococcal infections, particularly its long action following intramuscular injection. As a recent editorial (119) has emphasized, however, further experience is needed before this drug can be recommended as the one of choice, especially with respect to toxicity after parenteral use and to poor and variable adsorption after oral administration.

The present recommendations of the American Heart Association (107) for the prevention of rheumatic fever in rheumatic individuals are that all persons who have or have had rheumatic fever, chorea, or rheumatic heart disease should be placed on continuous prophylaxis for life. In patients with active rheumatic fever, penicillin should be employed to eradicate the streptococci before the prophylactic regime is instituted. The recommended prophylactic methods include one of the following: oral sulfadiazine, 0.5 gm. daily for children under 60 lbs., and 1.0 gm. for all others, each morning throughout the year; oral penicillin, 200,000 to 250,000 units once a day before breakfast; or intramuscular benzathine penicillin G, 1,200,000 units once a month. Due precautions should be taken to elicit a history of previous drug reactions and to observe the patients for the development of toxicity reactions.

Acute glomerulonephritis.—Like rheumatic fever, acute glomerulonephritis is a nonsuppurative complication of infection with Group A β-hemolytic streptococci. Unlike rheumatic fever, which presumably may follow infection with any type of Group A streptococcus, however, nephritis occurs principally after infection with strains of Lancefield's type 12 and less frequently with types 4, 25, and a new type named Red Lake (120 to 123).

The basic principles of prevention of first attacks of nephritis are the same as those for rheumatic fever, namely, early treatment of the streptococcal infection in order to eradicate the streptococci, or the prevention of the streptococcal infection entirely. In a controlled study of type 12 strepto-

coccal infections in a naval military establishment, Stetson and his associates (122) showed that penicillin therapy reduced the occurrence of nephritis to 4.5 per cent from an incidence of 11 per cent in the placebo or control group. Treatment consisted of an initial injection of 900,000 units of penicillin (450,000 units of crystalline procaine penicillin G and 150,000 units of crystalline potassium penicillin G per ml.) at the time of admission, followed by two injections of 600,000 units of procaine penicillin G in oil containing 2 per cent aluminum monostearate given two and four days later. Attempts to prevent streptococcal infection entirely in the general population are presently not feasible. At the time of epidemics of nephritis, however, prevention and control can be achieved (120, 121). Persons having close contact with the nephritic patient should be cultured, and those shown to harbor β-hemolytic streptococci should be treated with penicillin to eradicate the streptococci, in the same manner as recommended above for the treatment of streptococcal infections for the prevention of rheumatic fever (107). This procedure will limit the spread of infection.

The great majority of patients who develop acute nephritis after streptococcal infections recover completely and do not experience second attacks (121). A possible explanation may be that type-specific immunity follows the preceding streptococcal infection, and so few types of streptococci are nephritogenic that the likelihood is remote of a second infection with a different nephritogenic type. In any event, continual prophylaxis is not presently recommended for all patients recovered from acute glomerulonephritis.

Prevention of Infection with Bacteria in General

Subacute bacterial endocarditis.—Because transient bacteremia may occur after such operative procedures as dental extraction, tonsillectomy, childbirth, and prostatectomy, it has become standard practice to administer antibacterial agents to patients with rheumatic or congenital heart disease prior to these operations. The data which support the logic of this practice were reviewed by Finland (124), and little additional data have appeared since he pointed out that "the value of the procedure has never been proved, and the possible risks and dangers involved have never been evaluated."

Rhoads and co-authors (125, 126) found that 28.3 per cent of an unprotected group of patients had bacteremia following tonsillectomy. The incidence of bacteremia was not reduced in persons given 600,000 to 800,000 units of procaine penicillin 12 to 18 hr., and again 1 hr., before operation. Such a dose has reduced the incidence of bacteremia following tooth extractions from 38.2 to 5.8 per cent (125, 126) but probably does not provide the duration of action of the dosage (600,000 units each of aqueous penicillin and procaine penicillin in oil containing 2 per cent aluminum monostearate) recommended by the American Heart Association (107). No schedule of pretonsillectomy antibiotic therapy, including oral penicillin for five to seven days, had any effect in reducing the incidence of bacteremia except the daily injection of 600,000 to 800,000 units of procaine

penicillin for four to ten days prior to operation (125, 126). Study of the excised tonsils showed that this dosage of penicillin eradicated nearly all β-hemolytic streptococci and reduced the number of other gram-positive organisms except staphylococci and *Gaffkya tetragenus*. Moreover, staphylococci, and in addition, gram-negative organisms such as *Klebsiella pneumoniae*, *Aerobacter aerogenes*, and *Escherichia coli*, were found in increased numbers in cultures from the throat and excised tonsils. No complication attributable to these organisms occurred.

Respiratory diseases.—Despite the fact that antibiotics are of no value in viral respiratory diseases, these drugs are still widely used for this purpose. Some of the factors responsible for such unwarranted use were listed by Moulton (127): the assumption that antibiotics can do no harm, the belief that they are useful in preventing secondary bacterial infection, and the fact that accurate diagnosis is often difficult.

Walker (128) reported that prophylactic administration of tetracycline or oxytetracycline to institutionalized infants had no effect on incidence, duration, or severity of common respiratory infections. Traisman (129) administered various drugs and a placebo to children with colds. Complications, chiefly pneumonia and otitis media, occurred in the four groups as follows: control, 20 per cent; sulfisoxozole, 16.2 per cent; chlortetracycline, 11.4 per cent; penicillin, 18.7 per cent. In the control groups, 56 per cent of the children recovered within the first week and 73 per cent of the complications occurred during this time. In the treated groups, 39 per cent recovered and 37.5 per cent of the complications occurred within the first week. The net effect of chemotherapy, then, was to postpone the onset of complications and to prolong the total period of illness. Similar data were reported by Hardy & Traisman (130) with the recommendation that therapy be withheld until inception of the complication.

Poliomyelitis and measles.—Patients with poliomyelitis who have required a tracheotomy frequently develop pulmonary complications, one of which is bacterial pneumonia. A significant study of the effect of various antibiotics, singly or in combination, on the bacterial flora of the tracheal secretions of 72 such patients has been reported by Lepper *et al.* (131). The organisms found initially and during antibiotic prophylaxis were compared with those present during intervals when therapy was omitted. Since pneumococci, streptococci, and *Hemophilus influenzae* were readily eliminated and treatment of infections caused by them has been successful, the use of chemoprophylaxis to prevent infection with these organisms was felt not to be justified. The good that may be accomplished by prophylaxis is outweighed by the unfavorable alteration of the bacterial flora that was shown to be induced by the drugs.

Enterococci, *Streptococcus viridans*, and *Staphylococcus aureus* were no more frequent in treated than in untreated patients, although combinations of antibiotic drugs favored the implantation of new strains of staphylococci. Broad spectrum antibiotics facilitated the retention of resistant pseudo-

monas and proteus organisms. Treatment with any of the antimicrobial drugs favored implantation and retention of monilia. The authors concluded that it is preferable to follow the bacterial flora closely and to treat the complications as they arise.

Failure of antimicrobial agents to protect patients with bulbar involvement or respiratory muscle paralysis from bacterial infection has also been observed by Weinstein (102). In 165 patients who received no antibiotics, bacterial infections occurred in 16 per cent. Of 63 patients given chemoprophylaxis, bacterial complications occurred in 53 per cent. Pneumonia occurred in 6 per cent of the untreated and in 22 per cent of the treated patients, the organisms in the latter group usually being resistant to therapy.

Weinstein (132) similarly reported the failure of chemotherapy to prevent the development of bacterial infection during measles and suggested that the use of antimicrobial agents night have increased the risk of development of this complication. Of 130 patients with rubeola who were given antibiotics prior to admission, 30.4 per cent had bacterial complications at the time of admission. Of 298 cases not so treated, 14.9 per cent had bacterial infections. Of 350 cases given no therapy after admission to the hospital, 16 (4.6 per cent) developed bacterial disease. Of 94 patients treated after hospitalization (78 of these entered with complications), 11 (11.6 per cent) had evidence of a new bacterial infection. On the basis of these data, Weinstein (132) stated that "it appears not only unnecessary but also possibly even unwise to administer chemotherapeutic agents to patients with rubeola until there is definite evidence of a treatable secondary bacterial complication." Thus, the same conclusion has been drawn regarding the use of chemoprophylaxis for poliomyelitis and measles as was earlier reached for common respiratory infections.

Elective surgery.—One of the generally accepted indications for antibiotic therapy in surgical practice is the prophylactic administration of one or more drugs to patients subjected to surgical procedures performed through contaminated areas (133). Attempts to achieve relative sterilization of the bowel contents in preparation for surgery have continued (134 to 141), but these studies dealt largely with quantitative and qualitative changes in the fecal flora rather than with the postoperative courses of the patients. Since McKittrick & Wheelock (142) have previously reported that antibiotics did not reduce the frequency of sequelae in patients subjected to abdominal surgery, other such controlled studies are needed. Neomycin would appear to be the drug of choice, although simultaneous administration of one of the tetracyclines (134, 136, 140) or nystatin (137, 139, 141) has been recommended. More data are needed to establish that the benefits derived from prophylaxis, particularly with broad spectrum antibiotics, outweigh the dangers inherent in the creation of an "intestinal bacterial vacuum" (143) that may lead to staphylococcal enterocolitis (143 to 146).

Two studies of patients undergoing transurethral prostatic resections have shown that penicillin alone or in combination with streptomycin (147)

or chloramphenicol alone (148) had no effect on the postoperative febrile response. Simon *et al.* (147) reported that penicillin and streptomycin did reduce the incidence of fever subsequent to removal of the urethral catheter from 26.0 per cent to 9.8 per cent. With alternated controls, Appleton & Waisbren (148) demonstrated that prophylactic chloramphenicol had no beneficial effect on postoperative complications, bacteremia, hospital course, or mortality. Furthermore, there was evidence, as in the studies previously mentioned, that resistant organisms had been substituted for sensitive ones.

Evidence indicating the failure of chemoprophylaxis to achieve protection against the general bacterial population and attesting the danger inherent in so altering the bacterial flora is accumulating steadily. It is conceivable that much of such prophylaxis might soon be abandoned, antibiotics being withheld until there is a specific indication for their use.

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DISEASES OF THE GASTROINTESTINAL TRACT[1]

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In reviewing the publications of the past year devoted to disorders of the gastrointestinal tract the authors have attempted to integrate the articles presenting newer fundamental knowledge or basic concepts with the clinical presentations which offered the broadest scope to the physician in the diagnosis, treatment and understanding of these diseases.

Considerable attention this year has centered about the syndrome of metastasizing carcinoid tumors of the small intestine associated with right sided heart lesions and a high concentration of serotonin in the blood. There has been increased interest in studies of intestinal absorption utilizing isotope techniques, and continued investigation of the chemical and metabolic abnormalities in hepatic coma and its treatment. A number of stimulating articles have been devoted to hormonal and endocrine influences upon the stomach and a large number of publications have been concerned with chlorpromazine jaundice and intravenous cholangiography employing iodipamide (Cholografin).

ESOPHAGUS

Anatomy and physiology.—Continued interest in the esophagus is reflected by a comprehensive review of the normal anatomy and physiology presented by Wilner, Bandes & Hollander in an issue of the *Journal of the Mt. Sinai Hospital* devoted entirely to the esophagus (1). Fyke & Code (2) measured the normal resting and deglutition pressures in the pharynx and upper esophagus with a sensitive transducer. They demonstrated a large, though very transient, pressure gradient between the pharynx and upper esophagus, probably responsible for the rapid transport through this region.

The differentiation clinically between substernal cardiac pain and pain arising from esophageal disease is often difficult. Kramer & Hollander (3) studied the effects of balloon distention of the esophagus in normal subjects, and in patients with angina pectoris and esophageal disease. They observed a wide scatter of referral of pressure pain in normal subjects. Balloon distention reproduced anginal pain without concomitant electrocardiographic changes in cardiac patients, but did not consistently produce pain in patients with esophageal disease. The authors concluded that balloon distention of the esophagus was of little diagnostic value, as might be anticipated from Sir Thomas Lewis' theory of faulty localization of visceral pain.

Cardiospasm.—Reflux of gastric juice into the esophagus constitutes a

[1] The survey of literature pertaining to this review was completed in June, 1956.

serious complication in the surgical correction of cardiospasm. The effectiveness of the Heller procedure (extramucosal esophagomyotomy) in cardiospasm has been reviewed by Richman (4). Esophagitis developed at varying periods postoperatively in three of fifteen patients operated on by this technique which interferes less with the "cardiac sphincter" than do other procedures. In a review of the surgical approach to cardiospasm, Sweet (5) recommends esophagoplasty for cardiospasm with a thin atrophic mucosa terminally, and the Heller procedure for spasm with hypertrophy of the sphincter. Favorable results were reported with few complications of esophagitis after three or more years.

Hiatus hernia.—The symptoms of hiatus hernia are exceedingly variable depending upon the size of the hernia, reflux of gastric contents into the esophagus, and the presence of ulceration or inflammation. Minimal hiatus herniation often causes no symptoms (6). In a discussion of the surgical management of hiatus hernia, Lyons & Parodny (7) do not recommend surgery unless marked symptoms are present.

Peptic esophagitis.—The relationship between peptic esophagitis and hiatus hernia is well documented. In a review of this subject, Wolf *et al.* (8) further amplify reflux esophagitis, as defined originally by Allison and Barrett, by describing "marginal esophago-gastric ulceration" observed with gastric juice regurgitation and sliding hiatus hernia. Cross & Kay (9) reported a surgical series of 55 cases of peptic esophagitis, 41 of which were associated with hiatus hernia. They contend that the ideal surgical procedure for esophagitis should aim for a reduction of gastric acid and pepsin, spatial separation of the esophagus from the remaining acid and pepsin, and satisfactory gastric drainage. These principles have been applied with satisfactory short term results.

Esophageal stricture.—Fatti *et al.* (10) reviewed an extensive series of 147 corrosive strictures of the esophagus treated over a six-year period. Dilatation was attempted in 70 per cent, and esophago-gastrostomy was eventually necessary in 55 per cent. The mortality for the entire series was 9 per cent, a significant improvement over the 30 per cent mortality reported earlier. In cases of extensive stricture of the esophagus, Belts *et al.* (11) recommend surgical esophagojejunostomy with extra-pleural jejunal transplant and high anastomosis. Nine cases were reported, without a mortality, and with a good postoperative nutritional state.

Esophageal tumors.—The rapidly developing field of exfoliative cytology has been applied to esophageal carcinoma by Klayman (12). In a series of 40 patients with suspected esophageal disease, cytology proved correct in 19 of 20 carcinomas, and in all 20 benign lesions. Annual cytologic examination in cardiospasm is recommended since the two diseases may co-exist occasionally.

Klein & Garlock (13) reported their surgical experience in 401 patients with esophageal carcinoma. Emphasis is again directed toward the importance of distinguishing palliative from radical surgery in evaluating results.

It is further suggested that squamous carcinoma of the esophagus be considered independently from adenocarcinoma of the gastric fundus, since the former rarely spreads downward while gastric adenocarcinoma often invades the esophagus.

Diverticula.—The anatomy, pathogenesis and clinical features of esophageal diverticula have been reviewed by Cornell (14). Hawes & Walker (15) found severe secondary pulmonary disease in two cases of Zenker's diverticulum and emphasized the importance of excluding primary esophageal disease before performing surgery on a pulmonary lesion of unknown etiology.

Endoscopy.—Stempien *et al.* (16) have re-emphasized the value and ease of application of the flexible-tipped esophagoscope, a topic which has received little attention in the literature. The complementary role of esophagoscopy and x-ray is stressed.

STOMACH AND DUODENUM

Gastric Secretion

Experience with the tubeless method of detecting gastric acidity using an azure A ion exchange indicator (Diagnex improved) was described by Goldbloom *et al.* (17). The test was reported to give almost 100 per cent accuracy in the qualitative detection of free acidity when compared to gastric analysis. Galambos & Kirsner (18) noted a good correlation between the quinine method of tubeless gastric analysis and the one hour basal aspiration before and after irradiation of the stomach. However, Woodward *et al.* (19) found a lack of quantitative correlation in the one hour basal secretion.

Further experience with the blood pepsin determination has been reported by Spiro *et al.* (20). No definite relationship between blood pepsin and gastric acidity could be found although, in general, the blood pepsin was elevated in patients with high gastric secretory rates following histamine stimulation, and in duodenal and gastric ulcer.

Recent studies on uropepsin excretion have been reported by a number of observers. Levy & Levine (21) confirmed previous reports that uropepsin output was not altered by vagotomy. In general there was a decrease in output following subtotal gastrectomy, but this was not constant, and the fall was not proportional to the amount of stomach removed. A very thorough review of the literature on uropepsin excretion has been undertaken by Bridgewater *et al.* (22), who found that the uropepsin excretion rate was greater in males than females by an average of 60 per cent. Pre-adolescents had a significantly lower output than adults, and there was a decreased excretion rate in the age group over 60.

Hormonal influences upon the stomach continue to be of interest. Not only the adrenal gland, but the sex hormones as well appear to affect gastric activity. A further elaboration upon the effect of ACTH on the secretion of acid, pepsin, and electrolytes in gastric pouch dogs was reported by Villarreal *et al.* (23) who observed significant increases in the output of HCl, pepsin

and chlorides and a fall in sodium and potassium within four to six hours after the intramuscular administration of 25 units of ACTH. The effect was independent of the vagus nerve or gastric antrum and was not inhibited by acetazoleamide (Diamox). Kyle *et al.* (24) reported that gastric acidity after a test meal is increased in patients with Cushing's disease with a return to low or normal levels following adrenalectomy. A review of the effects of adrenocortical function and stress on gastric secretion and ulcer production has been presented by Gray and associates (25). Seven patients with Addison's disease who developed active gastric or duodenal ulcer during long term cortisone therapy are presented.

Balfour (26) reported that the daily intramuscular administration of 100 mg. of testosterone propionate in oil to healthy young men and to elderly males produced a significant increase in uropepsin excretion. The response was similar to, but not so great as the rise produced with ACTH or cortisone. The author concludes that testosterone, in addition to the adrenal glucocorticoid hormones, affects the basal state of gastric function. Changes in gastric activity during the menstrual cycle in normal human subjects have been reported by MacDonald (27). A gradual increase in gastric acidity was noted in the first half of the cycle with a slight decline during the second half; an increased rate of gastric emptying was found at the time of ovulation.

Various therapeutic agents, in addition to ACTH, which are known to reactivate or produce peptic ulceration have been studied in respect to gastric secretion. Phenylbutazone (Butazolidin) increased gastric acidity in 21 of 44 basal gastric analyses on 30 patients (28). The effect was not mediated via the vagus or adrenals but was attributed to a local irritant action on the parietal cells. A temporary increase in secretion, accompanied by erosions and acute ulcers, was also observed in gastric pouch dogs after prolonged intramuscular administration. Reserpine has also been shown to produce significant elevations in gastric acidity (29), while chlorpromazine hydrochloride (Thorazine) apparently had no effect.

The complex inter-relationships between emotional stimuli and gastric secretion have been the subject of two recent articles. An excellent study of the effect of hypnotically induced emotional reactions on gastric secretion was reported by Eichhorn & Tracktir (30). The gastric response to induced fear and anger varied depending on the underlying anxiety level. The highly anxious group showed an increased acid output during fear and a decreased output with anger, while subjects in the low anxiety group showed the reverse type of response. It was also noted that contentment induced during hypnosis resulted in the highest levels of gastric secretion in both groups. The gastric response to histamine may also be influenced by emotional states (31). During periods of active emotional reactions in a child with a gastric fistula, a greater hydrochloric acid secretion resulted following histamine stimulation than when the child was withdrawn, depressed, or asleep.

A very thorough study of the relative effectiveness of ten anticholinergic drugs on basal gastric secretion in human subjects was reported by Sun *et al.*

(32). The production of a gastric juice pH of 4.5 or higher was used as the criterion for antisecretory potency. In their study the short and long acting propantheline (Probanthine), mepiperphenidol bromide (Darstine), methscopolamine bromide (Pamine), and tricyclamol methylsulfate (Elorine) were most effective in producing periods of anacidity. Similar results were attained with atropine, methantheline bromide (Banthine), and a new agent scopolamine-*N*-butylbromide (SKF 1637) in some individuals.

An initial depression of gastric volume and acidity during the first 30 minutes following intravenous insulin with a subsequent rise in 45 minutes is reported by Olsen & Necheles (33). They postulate that this reflects a changing concentration of glucose in the vagal nuclei. Hirschowitz *et al.* (34) suggest that alcohol stimulates gastric secretion through two mechanisms: (*a*) a non-specific antral stimulus releasing gastrin and (*b*) a specific stimulation of central vagal nuclei via the blood stream.

Hollander & Janowitz (35) review the metabolic reactions within the parietal cell during the formation of HCl with emphasis upon the role of carbonic anhydrase, and the inhibitory effects of acetazoleamide. The inhibition of gastric secretion in the mouse stomach by the use of compounds which combine with the sulfhydryl groups of enzymes necessary for HCl formation has been studied further by Davenport *et al.* (36).

Peptic Ulcer

Etiology and pathogenesis.—Evaluation of the multiple facets in the etiology and pathogenesis of peptic ulcer disease includes a number of diverse considerations: psychogenic, environmental, constitutional, hormonal, neurogenic, enzymatic, vascular, inflammatory, chemical and specific blood groupings.

The incidence of ulcer disease in the United States Army for the years 1937 to 1953 varied between 1.5 to 3.4 per 1000 per year, and was highest during World II (1941 to 1944) and the Korean conflict [1950 to 1953 (37)]. However, the statistics demonstrate that combat was not a factor in the initiation of ulcer or its reactivation. Monotony, lack of motivation, and problems of adjustment were the most common aggravating factors. A thorough review of the literature in respect to the psychiatric approach to ulcer disease was presented by Roth (38). The conclusions derived from this study tend to dispel the concept of a specific ulcer personality.

Jones (39) discusses the constitutional, environmental, social, geographic, and occupational factors in peptic ulcer disease. From these studies he concluded that gastric and duodenal ulcer may have a different etiology, and that gastric hypersecretion in peptic ulcer disease may be related to a greater secretory cell mass. Winkelstein *et al.* (40) presented evidence that the continuous secretion of acid and pepsin in the empty or fasting stomach is conducive to duodenal ulcer formation in dogs. Dragstedt (41) suggested that gastric ulcers are caused by prolonged stimulation of the gastric antrum brought about by antral distention or pyloric stenosis. Studies by State *et al.*

(42), however, indicate that the presence of the antrum reduced the incidence of histamine-produced ulcers in dogs with 50 per cent wedge resections of the stomach.

An interesting study of a duodenal ulcer family in which 9 of the 13 living siblings had duodenal ulcer was reported by Wright *et al.* (43). The relationship of the ABO blood groups to duodenal and gastric ulceration has received further attention. Clarke *et al.* (44) noted a high frequency of blood group O in duodenal ulcer, but not in gastric ulcer. This was also reported by Koster *et al.* (45) who found, in addition, a high group A incidence and a low group O in gastric cancer.

Confirmation of the high incidence of peptic ulcer in pulmonary emphysema is reported by Latts *et al.* (46) who found peptic ulcers in 15 per cent of patients with emphysema and in 27 per cent of autopsy cases. Bleeding, perforation or obstruction occurred in 39 per cent of these ulcer patients. Although the cause is unknown, the authors speculate upon (*a*) correlation of carbon dioxide arterial tension with gastric hypersecretion, (*b*) emotional factors, and (*c*) chronic stress resulting from anoxia mediated to the stomach by way of an adrenal mechanism. Various case reports and reviews emphasize new ulcer formation or the reactivation of a pre-existing ulcer following the use of various therapeutic agents including ACTH (47), prednisone [Meticorten (48)], acetylsalicylic acid (49), and phenylbutazone (28).

Diagnosis.—The clinical picture of pyloric channel ulcer has been described by Ruffin *et al.* (50) in a review of 100 cases. The symptoms are generally atypical for ulcer disease with frequent nausea, vomiting, pain unrelated to meals, and weight loss. The symptoms of posterior penetrating gastric ulcer are described by Caruolo *et al.* (51). The most common complaints were epigastric and back pain, vomiting, and bleeding. The origin of pain in peptic ulcer disease was reviewed by Smith (52), who believes that the local inflammatory reaction is the predominant factor rather than the degree of acidity or hypermotility. Johnson (53) reports on the occurrence of co-existent gastric and duodenal ulcers in a series of 130 cases. In 93 per cent the duodenal ulcer occurred first. He believes that pyloric stenosis and gastric retention are predisposing factors in the subsequent development of gastric ulcers which are usually large, bleed easily, and are rather resistant to therapy.

Medical therapy.—Miller & Berkowitz (54) analyzed the results of medical and surgical therapy in peptic ulcer in 729 clinic patients and in 300 private patients. A satisfactory remission was achieved by medical therapy or by a combined medical and surgical approach in 62.3 per cent of the clinic patients and in 92.3 per cent of the private patient group. Doll *et al.* (55) report no difference in the rate of healing of uncomplicated gastric ulcer treated by continuous intragastric drip compared with the usual ulcer management. The rate of healing was the same with a six-meal normal diet as with an eight-meal bland diet (56). Sun & Shay (57) emphasize the necessity of utilizing the optimal effective dose of the newer anticholinergic drugs in

treating ulcer patients. They recommend individualizing the amount of drug administered to achieve a gastric juice pH of 4.5 or above.

Surgical management.—Henson & Rob (58) reported a recurrence rate of 12 per cent in a series of 100 patients treated by vagotomy and gastroenterostomy, with a high incidence of postoperative symptoms (39 per cent). In Hoerr's (59) series of 145 duodenal ulcer patients treated by posterior gastroenterostomy and vagus section, 21 were considered failures, 12 patients developing recurrent ulceration. This procedure is recommended for the poor risk patient or when the technical situation makes gastric resection hazardous. In a review of the recurrence of duodenal ulcer after combined vagotomy and gastroenterostomy Oberhelman & Dragstedt (60) found that a high-lying enterostomy with vagotomy produced stasis and deposition of food in the antrum with a subsequent increase in gastric secretion. A stoma low in the antrum within 4 to 5 cm. of the pylorus is recommended.

Zollinger & Williams (61) review the various types of gastric resection and discuss means to avoid dumping symptoms. In their experience the resection of 50 per cent of the stomach combined with vagotomy and a Billroth I type of anastomosis, with a small stoma, resulted in better absorption of fat and protein and fewer dumping symptoms than the Billroth II operation. Thorn *et al.* (62) re-emphasize the increased incidence of pulmonary tuberculosis found in patients following subtotal gastrectomy. There was an increased risk in males who were below their normal weight at the time of operation and who failed to gain in the postoperative period. A greater incidence of tuberculosis was reported following resection for gastric ulcer than for duodenal.

Postoperative complications.—A high incidence of complications following gastric resection was reported by Morey & Plummer (63) in a study of 74 patients. In this series 36 patients developed mild to severe complications including the dumping syndrome, marginal ulcer, recurrent hemorrhage, and miscellaneous disturbances such as impaired gastric motility and iron deficiency anemia.

Polak & Pontes (64) believe that post-gastrectomy steatorrhea is caused primarily by the poor mixing of bile with the food, as a result of too rapid transit. They recommend the use of ox bile extract in large doses. The effect of gastric surgery on fat and nitrogen absorption in the dog was studied by Javid (65). Two-thirds gastrectomy increased the fat content in the stools from a normal level of 5.0 per cent to 17.1 per cent, and the nitrogen content from 13.6 per cent to 26.2 per cent. A further increase in fat and nitrogen loss occurred when vagotomy was combined with gastrectomy. Vagotomy alone, gastroenterostomy, or both, resulted in less nutritional disturbance. Wallensten (66) noted that many patients with post-cibal symptoms following subtotal gastrectomy had reduced serum iron and hemoglobin levels. In some cases these could be corrected by restoring the serum iron to normal. The incidence of megaloblastic anemia after total gastrectomy was reviewed by MacLean & Sundberg (67). They report that 10 out of 11 cases studied

developed a megaloblastic bone marrow three years after total gastrectomy. The anemia responded to vitamin B_{12} therapy in all instances.

Hemorrhage.—The diagnosis and management of upper gastrointestinal bleeding continues to present a problem and has been the subject of frequent studies in the past year. Zamcheck (68) presented a practical guide to the handling of this emergency in a large general hospital with particular emphasis on the use of diagnostic procedures to distinguish bleeding esophageal varices from peptic ulcer or hemorrhagic gastritis. In a review of over 2000 patients with hematemesis, melena, or both, Jones (69) reports a mortality of 15.9 per cent for chronic gastric ulcer in patients over 60, and a mortality of 2.5 per cent among those with acute lesions. Acute gastric ulcers were demonstrated in many cases by gastroscopy performed soon after the bleeding episode. Welch *et al.* (70) report a slight increase in mortality from ulcer hemorrhage treated medically, surgically, or in combination, from the decade 1923 to 1932 to the present. This rise is attributed chiefly to the increasing age of the hospital population and to postoperative complications; the authors advise earlier surgery in the elderly patient. Berkowitz *et al.* (71) reported an over-all mortality of 6.6 per cent in 373 patients with bleeding peptic ulcer. Eighty-four per cent of the deaths occurred in patients over 45 years of age. The mortality from bleeding gastric ulcer was considerably higher than that of duodenal ulcer. The highest mortality occurred with the first or second hemorrhage.

Gastrointestinal bleeding may reflect a number of disease processes other than peptic ulcer and esophageal varices. In a series of three articles Brick & Jeghers (72) made an extensive survey of the literature dealing with the less common causes of gastrointestinal hemorrhage such as hiatus hernia, gastritis, prolapsed gastric mucosa, Mallory-Weiss syndrome, diverticula, polyps, ulcerative esophagitis, etc. Wechsler *et al.* (73) describe a method for detecting impending shock by tilting the head of the patient's bed at an angle of 60°–90°, and observing an increase in pulse rate and drop in blood pressure. They also report their experience with radioactive chromium in the measurement of red cell mass and plasma volume as an aid in blood replacement therapy. A rather unique method of arresting duodenal and gastric bleeding is reported by Brandon (74) who utilizes a combination of epinephrine and Russell's viper venom (Stypven) instilled through a gastric tube.

Two recent studies deal with the relationship of upper gastrointestinal bleeding with acute intracranial lesions. Cabieses & Garrido-Lecca (75) report 10 patients with acute neurosurgical lesions in the vicinity of the third ventricle who developed upper gastrointestinal bleeding. Doig & Shafar (76) describe seven patients with gastric bleeding associated with intracranial hemorrhage. The literature on the relationship of intracranial lesions to gastric erosions and ulcers is reviewed. The authors believe that vascular changes in the gastric mucosa are followed by necrosis, and acute ulceration.

Cohn *et al.* (77) conclude that significant azotemia in gastrointestinal bleeding depends upon reduced renal function secondary to diminished circu-

lating blood volume, or to pre-existing renal disease, rather than to the absorption of nitrogenous products from digested blood.

Perforation.—Jamieson (78) made a survey of the incidence of perforated peptic ulcer in the Glasgow area for the period 1944 to 1953 and compared this with a previously published study covering the years 1924 to 1943. The yearly rate per 100,000 population had increased from 11 to 33. The author estimates that 1 to 2 per cent of adult males with peptic ulcer perforated annually. Fatigue was suggested as an etiological factor. Bisgard (79) reviewed the literature on the surgical management of perforated ulcer and found a recurrence of ulcer disease in 70 per cent within five years of simple closure of the perforation. He recommends more frequent emergency gastric resections in these cases.

In the treatment of perforated acute peptic ulcers Taylor & Warren (80) recommend conservative therapy by aspiration and antibiotics, since in their experience with 47 such cases there were no fatalities and no subsequent complications. They recommend gastric resection, however, for all perforated chronic peptic ulcers.

Pyloric obstruction.—A detailed program for the medical management of obstructive peptic ulcer, presumably on the basis of edema and spasm rather than cicatrix or stenosis, was presented by Marshall *et al.* (81). Only seven of 201 patients failed to respond to intensive medical therapy, and at exploration true stenosis was found.

Gastric Cancer

Gastric cancer remains an enigma. Newer diagnostic methods and surgical techniques are reported, but no fundamental advances are apparent. Gastric cancer was the subject of a symposium presented at the Sixth National Gastrointestinal Cancer Conference and reviewed in the October, 1955 issue of *Gastroenterology*. Macklin (82) reported a greater frequency of gastric cancer (4.8 times the control) among close relatives of gastric cancer patients, indicating a significant hereditary factor. Shahon *et al.* (83) found achlorhydria or hypochlorhydria in 87.8 per cent, and occult blood in the stools of 83.2 per cent of patients with gastric cancer. The five-year survival rate had increased from 3.7 per cent (1936 to 1939) to 12.5 per cent during the period 1946 to 1949. In a nine and one-half year follow up of 3516 patients over the age of 50 with histamine achlorhydria, hypochlorhydria, or pernicious anemia, Hitchcock *et al.* (84) found 38 gastric cancers, a significantly higher incidence than in the population at large. Zamcheck *et al.* (85) reported a 10 per cent cancer incidence among 1222 patients with pernicious anemia observed from 1915 to 1951.

Klayman *et al.* (86) summarized their experience with gastric exfoliative cytology in the diagnosis of gastric malignancy. Chymotrypsin lavage appeared more accurate than the gastric brush or the abrasive balloon. The use of the urinary uropepsin tests as a diagnostic aid in gastric cancer detection was suggested by Gray and associates (87). In the presence of gastric ulcer a

uropepsin excretion below 1000 units indicated a high probability of cancer. Nakayama (88) described a technique of diagnosing gastric cancer with an intragastric Geiger counter, based on the selective uptake of radioactive phosphorus by gastric cancer.

Grant & Ivy (89) studied the sequence of histological changes in the stomach of rats following the embedding of hydrocarbon carcinogens into the gastric submucosa. Black *et al.* (90) re-evaluated the histological appearance of the tumors and surrounding lymph nodes in an attempt to establish criteria which might serve as an index for host resistance to tumor growth and host survival. Hay (91) reviewed the surgical management of gastric polyps and adenomas. In his experience the tendency towards malignant degeneration in small polyps (less than 2 cm. in diameter) was much less than in the larger variety. Ransom (92) concluded from a study of 118 patients that total gastrectomy for gastric cancer yielded no better results than radical subtotal resection.

SMALL INTESTINE

Intestinal Absorption

Radioactive isotopes.—The use of radioactive isotopes in evaluating intestinal absorption represents a distinct advance in this field, although the difficulties inherent to all intestinal tolerance tests still present a challenge. Stanley & Cheng (93) have developed a promising method for measuring cholesterol exchange utilizing C^{14} labelled cholesterol, with chromic oxide as an inert indicator. Benson (94) investigated the absorptive capacity of various levels of the small intestine for neutral fat, using radio I^{131} labelled olive oil in rats. Optimal absorption of the radio fat was noted in the third quarter of the rat intestine. Halsted *et al.* (95) reported a defect of radioactive B^{12} absorption in two patients with megaloblastic macrocytic anemia presenting certain intestinal abnormalities. Abnormal bacterial flora in the small intestine resulting from stricture, anastomosis, or fistula may interfere with B^{12} utilization on the basis of competitive activity. Normal radioactive B^{12} absorption was observed after the administration of broad spectrum antibiotics.

Glucose.—The variability of the oral glucose tolerance curve is stressed by Test *et al.* (96) who demonstrated that flat glucose tolerance curves reverted to normal in 15 of 26 subjects when the test was repeated. No relationship was found between a flat curve and the rate of gastric emptying. A persistent flat oral glucose tolerance curve, however, reflected a defect in intestinal absorption. Cummins & Jussila (97) compared glucose absorption rates in the upper and lower human small bowel, using 5 and 10 per cent glucose and 5 and 15 per cent urea solutions and demonstrated a gradient of absorption. The lower small bowel absorbed significantly less of both the glucose and urea solutions.

Sprue and Related Syndromes

The beneficial effects of ACTH and the adrenal steroids in the treatment of the sprue syndrome and the significance of dietary gluten have received considerable attention in recent years. In their reviews Paterson (98), Frazer (99), and Sheldon (100) emphasize the importance of gluten intolerance in celiac disease. The potentially chronic nature of this disease was assessed by Lindsay *et al.* (101) who reevaluated 25 adults who had celiac disease in childhood 15 years previously. Four presented evidence of active disease, and four others revealed minor degrees of malabsorption.

The adrenal steroids not only may induce a clinical remission in the sprue syndrome but definitely improve the intestinal absorption of fat, nitrogen, and calcium. An improvement in vitamin A, glucose, and iron absorption may be noted after 15 days, although the absorption curves do not always return completely to normal within this period (102).

Whipple's disease.—Puite & Tesluck (103) reported four new cases of this disease, with two patients, and possibly a third, appearing in one family. The question of genetic transmission is raised. Wang *et al.* (104) observed a patient with intestinal lipodystrophy who improved clinically on steroid therapy. After the third course of steroids, a 20-month remission ensued, and intestinal absorption returned to normal. This report, and the documented response of other patients with Whipple's disease to steroid therapy suggest that this hitherto hopeless disease may be amenable to treatment in some instances.

Regional Ileitis

This disease has been the subject of a recent comprehensive review by Zetzel (105). The pathological distinction between regional ileitis and ulcerative colitis has been the subject of considerable discussion during past years. Otani (106) describes a histologically distinctive pure regional ileitis, pure ulcerative colitis and a granulomatous process involving both the small intestine and large bowel, classified as regional enterocolitis. The clinical aspects of combined ileocolitis have been discussed by Yarnis (107) who emphasizes again that surgery during the acute phase of this disease is almost always followed by recurrence.

Regional enteritis is not restricted to the small intestine alone but may involve the stomach and duodenum as well. The interesting picture of granulomatous involvement of the stomach and duodenum in patients with regional enteritis has been reviewed by Richman *et al.* (108). Fistulae in such cases are apparently rare. The major symptoms seem to be the result of pyloric and duodenal obstruction.

The extra-intestinal manifestations of regional ileitis apparently are less common than similar complications in ulcerative colitis (109). The liver in regional ileitis is usually involved to a lesser degree than in ulcerative colitis (110). Chapin *et al.* (111), however, reviewing 30 cases of ileitis at postmor-

tem, found a relatively high incidence of peritonitis, fatty liver, glomerulitis, or renal tubular degeneration, which may be attributable to any severe debilitating disease. Ginzburg (112) recommends surgery only for complications such as perforation or obstruction, rather than for ileitis per se. Resection or enterocolostomy with exclusion are equally preferable in his experience.

Small Bowel Tumors

The curious syndrome of malignant carcinoid tumor of the intestine accompanied by right-sided valvular lesions of the heart, a peculiar type of flushing, and occasionally diarrhea has aroused considerable interest. It has been suggested that the cause of the symptoms may be the secretion of 5-hydroxytryptamine (serotonin) by the tumor. Patients with malignant carcinoids metastasizing to the liver demonstrate abnormally high concentrations of 5-hydroxytryptamine in the blood and 5-hydroxy-indole-acetic acid in the urine (113 to 116). Snow *et al.* (113) found a general relationship between the severity of the symptoms and the amount of serotonin in the blood. No improvement, however, followed the administration of substances which act as serotonin antimetabolites. A simple urinary screening test for the presence of 5-hydroxy-indole-acetic acid has been reported by Hanson & Serin (114), who also have described a quantitative urinary method which may be helpful in the diagnosis of malignant carcinoids.

Spain (115) analyzed a series of 26 autopsy-proven cases, and found a high incidence of cardiovascular abnormalities. The most pronounced valvular involvement (tricuspid and pulmonic valves) was observed in the cases with metastases. A surgical series of 25 carcinoid tumors, nine of which were appendiceal, has also been reported (116). Metastasizing tumors arose from the extra-appendiceal primary sites in all cases but one.

Primary Jejunal Ulceration

Zollinger & Ellison (117) have reported two interesting cases of primary jejunal ulceration with marked gastric hypersecretion, persisting after subtotal gastric resection, and with the subsequent finding of nonspecific islet cell tumors of the pancreas in both cases. A pancreatic ulcerogenic factor of humoral nature similar to glucagon has been postulated. One patient had a serum fraction similar to glucagon on electrophoretic study. Since the urinary 17-hydroxycorticoids have been noted to be elevated following intravenous glucagon, one wonders whether the ulceration may reflect adrenal stimulation from glucagon itself as an alternative hypothesis to a primary pancreatic hormonal effect on gastric secretion.

COLON AND RECTUM

Cancer

More frequent digital and sigmoidoscopic examinations and careful attention to the clinical history have resulted in earlier diagnosis and a

brighter outlook for cancer of the colon and rectum. The clinical evaluation of 750 patients with colon cancer seen over a 15-year period, has been reviewed by Shallow *et al.* (118). Fifty per cent of these cancers were palpable on digital examination. The classical symptoms of weight loss and anemia characterized the right sided lesions, while obstruction was more common in cancer of the left colon. Change in bowel habit was the earliest symptom of the malignant process, although it may occur late in the disease or may be absent. It should be emphasized that cancer may be present without producing any symptoms.

Successive independent carcinomas of the colon developing in 25 patients were reported by Ginzburg & Dreiling (119). The interval between the clinical manifestations of the successive malignancies varied from one to 23 years. Resection of the second neoplasm was feasible in 23 instances. Recurrent symptoms in a patient previously operated on for carcinoma warrants intensive investigation for the possible presence of a new and independent carcinoma. Beal & Cornell (120) considered the problem of the recurrence of carcinoma at the anastomotic site, following resection for primary malignancy of the bowel. Twenty-one recurrences in 140 patients extending over a five-year period were reported with a greater incidence following surgery of the left colon. Recurrent carcinoma was attributed to overlooked polyps which subsequently developed into carcinoma, and implantation of exfoliative cells at the time of the initial operative procedure.

The value of exfoliative cytology in the diagnosis of colonic carcinoma has again been emphasized. Galambos & Klayman (121) reported the successful use of this procedure following colonic irrigations in 68 patients. The practical aspects of the care of the sigmoid colostomy have been reviewed by Lyons (122). Equally important, Dyk & Sutherland (123) have reviewed the social and emotional problems relating to colostomy. Welch, McKittrick & Behringer (124), reviewing a series of 322 polyps treated over a 15-year period, found that 19 per cent proved to be carcinoma on the basis of microscopic examination. Three-quarters of these malignancies were within reach of the sigmoidoscope. The authors favor radical resection of the rectum, with or without sphincter preservation, if the lesion is papillary adenoma histologically or an adenomatous polyp with greater than Grade I malignant change. On the other hand, simple polypectomy with careful follow-up is recommended for benign polyps, cancer *in situ*, or malignancies considered to be Grade I or less. Segmental resection is considered the procedure of choice for benign polyps above the pelvic brim.

Lillehei & Wangensteen (125) have advocated total or subtotal colectomy for carcinoma or multiple polyps of the large bowel. A series of 73 patients is reported with a mortality of 5.5 per cent. They justify this radical approach because of the high incidence of unexpected multiple polyps of the colon (38 per cent) found in patients explored for either carcinoma or a single polyp. In their series, 18.6 per cent of patients with carcinoma of the colon either developed a second carcinoma subsequently, or an additional and independent unsuspected carcinoma was found at surgery.

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Ulcerative Colitis

Although the psychogenic factors in ulcerative colitis have been studied for many years and the adverse effects of emotional disturbances on colonic function well documented, a specific personality defect has never been established. In addition, it is difficult to determine whether the personality disturbance is the result or the cause of the disease. Psychotherapy, moreover, has not been impressive generally in the treatment. Engel (126) discusses the nature of the psychological process in ulcerative colitis in an extensive study of 39 patients personally treated by him, as well as a review of 700 cases in the literature. He accounts for the choice of the end organ (colon) on the basis of the "constitutional and experiential factors in the mother-child transaction." Consistently Engel has noted personality defects antedating the disease. Generally, these patients appear as dependent, restricted individuals, "lacking full heterosexual development."

Lieberthal & Frank (127), however, reported a case of ulcerative colitis in a Mongolian idiot. This typical Mongolian child was a happy, unintrusive and relatively undifferentiated personality, in contrast to the usual ulcerative personality type stressed by Engel. Five patients with intractable bowel disease associated with varying degrees of psychiatric dysfunction were subjected to prefrontal lobotomy (128). A complete remission of the colitis was reported in three, although spontaneous remissions and the small number of cases studied must be considered in the evaluation.

Galambos *et al.* (129) have studied exfoliative cytology in both acute and chronic ulcerative colitis. In the chronic disease large columnar cells were noted, which simulated malignant cells. Thus, cytological studies appear to be of limited value in diagnosing cancer in the ulcerative colitis patient. Rectal biopsies from patients with ulcerative colitis were compared with a normal series by Lumb & Protheroe (130). The earliest active lesions appear in the base of the crypts, with development of typical crypt abscesses. A significant alteration in the integrity of the basement membrane is demonstrable by histological and histochemical techniques in ulcerative colitis, although it is not specific for this disease (131).

Amebiasis

A seminar has been devoted to the choice of therapy in intestinal parasitic disease, with particular reference to amebiasis (132). A series of 75 patients with proven *endamoeba histolytica* was studied by Brown *et al.* (133), who reported the use of a new amebicidal agent, arsthinol (Balarsen). Thirty-one of 34 patients receiving the drug demonstrated negative stools on repeated examination one to 15 months later. Further investigation of this agent seems warranted. Amebic granuloma of the intestine has been discussed by Radke (134), with a review of 78 cases. The most common sites of involvement were the rectum and cecum. Symptoms appear to be similar to those of amebiasis with, however, a high incidence of intestinal obstruction.

The dangers of surgery in such cases are strongly underlined because of a mortality rate exceeding 60 per cent.

Hirschsprung's Disease (Congenital Megacolon)

This disease is characterized by a functionally abnormal, narrowed segment of bowel involving the rectosigmoid or rectum with a dilated, hypertrophied colon above. There is a complete absence of ganglion cells from the myenteric plexus in the spastic narrowed segment. Swenson *et al.* (135) found rectal biopsies to be an aid in the diagnosis of Hirschsprung's disease, particularly in the newborn where the entire colon may be aganglionic, and where the spastic segment may be two low for x-ray visualization. The authors advocate the use of multiple histological sections. Davidson *et al.* (136) studied distal colonic motility in children with megacolon, using electromanometric techniques recording the pressure fluctuations of the distal bowel. They believe that this technique may be more sensitive than x-ray in the demonstration of the transition zone between the normal and abnormal bowel in this disease. In contrast to cardiospasm where methacholine chloride (Mecholyl) produces severe spasm of the esophagus there is no such similar "Cannon effect" in Hirschsprung's disease because of the congenital absence of nerve plexi.

LIVER DISEASE

Circulation

The phrenic arteries may contribute significantly to liver blood flow under certain conditions. Jefferson *et al.* (137) demonstrated numerous good-sized anastomoses between the phrenic and hepatic arteries in corrosion specimens of dogs' livers following prior excision of the hepatic artery. In normal dogs, these anastomoses were insignificant. The importance of these communications is further emphasized by the experimental production of liver necrosis following intrahepatic block of the hepatic artery with vinyl acetate which apparently occludes these intrahepatic communications (138). Intrahepatic block of the portal vein by this method caused no significant damage to the liver. Ligation of the portal vein, however, produced cyanosis of the bowel, shock, and rapid death of dogs (139). It is of considerable interest that the portal vein could be ligated and cut after a few days without producing an acute fatality following prior ligation of the common duct, cholecystectomy, and excision of the hepatic artery. It was postulated that the distended biliary radicles compressed the terminal hepatic branches of the portal vein, thus allowing time for development of a collateral circulation between the portal and systemic vessels.

Studies of the circulation of the liver with P^{32} labelled colloidal chromic phosphate demonstrate clearance of this compound from the circulation of the isolated rat liver preparation according to a single exponential term of time (140). These studies establish a specific function of the liver dependent upon blood flow distribution within the organ.

The genesis of shock in hepatic necrosis is attributed by State & Lichtenstein (141) primarily to hemorrhage into the hypoxic liver with a subsequent decrease in the effective circulating blood volume. Fisher *et al.* (142), studying arterialized livers (aorta and portal vein anastomoses) in animals, demonstrated an initial elevation of hepatic blood flow which returned to control levels in 30 days, presumably because of a decrease in the size of the shunt. Bishop and his associates (143) found that the hepatic oxygen A-V differences were increased in all patients with rheumatic heart disease during exercise, on the basis of a decrease in hepatic blood flow, and postulated that the low O_2 saturation of hepatic venous blood may be concerned in development of cardiac cirrhosis of the liver. Eisenberg (144) measured the red cell mass and plasma volume in 20 patients with Laennec's cirrhosis utilizing red cells labelled with radioactive chromium. There was a significant increase in plasma volume only in patients with esophageal varices or cyanosis. Bernhard, McMurrey & Curtis (145) demonstrated the feasibility of partial hepatic resection under hypothermia in dogs.

Biochemistry

Interest in copper metabolism in hepatolenticular degeneration continues. Dialysis equilibrium experiments and electrophoretic studies suggest that the mechanism of copper deposition in the liver of patients with hepatolenticular degeneration is caused by an abnormality in protein metabolism leading to the formation of proteins with high copper avidity (146).

Volwiler *et al.* (147) emphasize the technical difficulties of measuring turnover rates of plasma proteins with radioactive isotopes. Fibrinogen and beta-1 lipoprotein presented a more rapid turnover rate than albumin, gamma globulin, or total serum proteins. The beta-1 lipoproteins appear to have a slightly longer biologic life span in cirrhotic patients. Klatskin & Bungards (148) conclude from filter paper electrophoresis that most of the bilirubin in the serum is bound to albumin irrespective of its behavior in the Van den Bergh reaction. They found no evidence that globin remains attached to the prosthetic group to yield indirect reacting bilirubin, and demonstrate that the two types of Van den Bergh reaction are not related to differences in bilirubin-protein linkage. Studies on the origin of bile pigment indicate that in normal man at least 10 to 15 per cent of the total bile pigment is derived from sources other than the hemoglobin of mature circulating erythrocytes (149). Horner-Andrews (150) discusses the interesting hypothesis that the biliary epithelium secretes most if not all the constituents of the bile, although no laboratory evidence is presented.

Endocrine Influences

Several papers present further evidence that the adrenal gland is implicated in fat metabolism of the liver. Perry & Bowen (151), investigating the metabolism of C^{14} tagged acetate in liver slices from intact and adrenalectomized rats, demonstrated a decreased rate of incorporation of this com-

pound into fatty acids, cholesterol and carbon dioxide in adrenalectomized animals. This decrease was attributed to either diminished synthesis or increased turnover by the liver.

Mallov & Block (152) showed that fatty infiltration of rat livers following alcohol intoxication did not occur in adrenalectomized or hypophysectomized animals. With cortisone administration, however, fat accumulated in the organ. Rabbits given 10 mg. of cortisone intramuscularly daily for 14 days, or epinephrine with cortisone presented a 300 per cent increase in liver weight, and an increase in the lipide fractions, particularly the phospholipides and the neutral fat (153). Tanyol & Rehfuss (154) noted that cortisone increased the extent and severity of liver damage in rats poisoned with carbon tetrachloride. Varying degrees of hepatocellular degeneration and necrosis were demonstrated in a limited number of normal rats given cortisone alone in maximal doses. Mayer *et al.* (155) studied fat metabolism in three types of obesity in animals [(*a*) genetic, (*b*) goldthioglucose, and (*c*) hypothalamic] and found that liver slices from all three types exhibited greater lipogenesis than normal.

Chart *et al.* (156) incubated the salt-retaining hormone aldosterone with rat liver slices and found that the biological potency of the steroid was completely inactivated. It is implied that impaired liver function may lead to abnormal accumulation of this hormone in the blood, tissues, and urine.

Liver Function Tests

Much confusion still exists in the interpretation and selection of liver function tests. Zieve & Hill (157) applied statistical methods to a large group of the commonly used liver function tests in an attempt to correlate mathematically their relative value, alone and in combination, in differentiating normal function from that found with cirrhosis and acute viral hepatitis. The sulfobromophthalein test proved to be the single most effective procedure in cirrhosis, while the lowest intercorrelation was found with the urine coproporphyrin determination. The effectiveness of each test in discriminating between cirrhosis and normals was dependent upon four sets of fundamental factors represented by the sulfobromophthalein, zinc sulfate turbidity, intravenous hippuric acid synthesis, and urine coproporphyrin tests. Each of these contributed independent information. In acute viral hepatitis these four tests were again the most effective, but individually the sulfobromophthalein and urinary coproporphyrin were the best. As a group, however, the highest inter-correlation among tests in acute hepatitis was observed with the urinary coproporphyrin and cholesterol ester determinations.

Glucagon.—Van Itallie & Bentley (158) investigated the hyperglycemic ability of glucagon (hyperglycemic glycogenolytic factor of the pancreas) as an index of liver function. The glucagon test alone was of little value. However, when epinephrine, which may inhibit the uptake of glucose by the peripheral cells, was given before glucagon, the test appeared to have

potential value. Cohen *et al.* (159) showed that sulfobromophthalein has a greater affinity than rose bengal for the transfer mechanism concerned in the removal of dyes from the circulation and their excretion in the bile.

Transaminase.—The serum glutamic oxalacetic transaminase level as an index of liver cell injury has been studied recently (160). This enzyme is present in the liver as well as in the heart muscle, brain, and kidney. The transaminase level is elevated following acute liver cell injury (carbon tetrachloride), infectious hepatitis or homologous serum jaundice and may be a sensitive index of liver metastases. There is no consistent pattern, however, with chronic liver disease. The transaminase level measures liver cell destruction and does not correlate well with the usual liver function tests. An elevated value may appear one to four weeks before other clinical or laboratory evidence of liver injury becomes manifest.

Serum iron.—The serum iron level continues to be of interest (161). The internal redistribution of iron in the body is controlled partly by the liver and has been studied rather extensively during recent years. The serum iron level is elevated in acute viral hepatitis, liver cell necrosis, hemolytic disease, iron storage disease and pernicious anemia, and is essentially normal in obstructive jaundice and cirrhosis.

Cirrhosis of the Liver

Treatment.—There have been a number of articles on the treatment of cirrhosis (162 to 165). Davidson emphasizes sodium restriction (200 mg. daily) in patients with ascites (163). In general, a high carbohydrate diet supplying 2000 to 2500 calories per day with 70 gm. of protein is recommended. In coma or pre-comatose states, the protein is reduced to approximately 50 gm. per day or may be eliminated altogether. At the present time there is no good evidence to support the use of ACTH or adrenal steroids in the treatment of the average patient with chronic liver disease, although either may be helpful in severe and prolonged anorexia (164). Roberts *et al.* (165) emphasize the importance of electrolyte disturbances and the use of exchange resins, diuretics, and sodium restriction in the control of ascites. The dangers of potassium depletion following the administration of diuretics are discussed.

Leevy *et al.* (166) in evaluating serial liver biopsies in 237 patients with various types of liver disease concluded that fibrosis, when not too severe, is not necessarily progressive and may be influenced by treatment, while severe fibrosis is usually refractory in spite of laboratory and clinical improvement.

Dietary factors.—Further evidence is presented that the daily fat intake of patients with fatty cirrhosis or viral hepatitis need not be restricted if the diet is adequate in protein, lipotropic substances and calories. Mindrum & Schiff (167) performed serial liver biopsies on alcoholics with fatty livers who were given 300 gm. of fat daily in addition to the regular hospital diet. They demonstrated clinical improvement and disappearance of excess liver fat histologically despite the high fat intake. Oral protein feeding was accom-

panied by an increased splanchnic blood flow, splanchnic oxygen consumption, and arterio-hepatic vein oxygen difference in both normal and cirrhotic subjects. The changes were less marked and more delayed in the cirrhotics. Moreover, the amino acid nitrogen levels in the peripheral and hepatic vein blood were higher than normal in cirrhotics after protein feeding. Brandt *et al.* (168) concluded that a high protein diet increased the work of the liver, and recommend a nutritious diet with a quantity of protein sufficient to maintain the patient in positive nitrogen balance.

Esophageal Varices

The successful treatment of esophageal varices by shunt procedures was reported by Linton & Ellis (169). In 78 patients with cirrhosis and bleeding esophageal varices in whom splenorenal or portacaval shunts were performed no recurrent bleeding was seen in 83 per cent in a one- to eight-year follow-up. The most effective emergency control of massive bleeding was by cardio-esophageal tamponade with an intragastric balloon, supplemented, if necessary, by transpleural transesophageal suture of the varices (169).

Although Linton *et al.* (170, 173) prefer splenorenal shunt for intrahepatic portal block caused by cirrhosis, Blakemore (171) favors the portacaval anastomosis. Julian (172) recommends splenorenal anastomosis for: (*a*) extrahepatic obstruction, in which the portal vein is diseased, (*b*) chronic obstructive cholangitis, and (*c*) patients with extensive biliary tract surgery. He believes that portacaval anastomosis is preferable in intrahepatic disease.

In a follow-up of 125 patients one to ten years after shunt procedures for bleeding varices Ellis, Linton & Jones (170) reported an over-all mortality of 29 per cent and an operative mortality of 11 per cent. The bleeding incidence was reduced and life prolonged. A decrease in the size of the varices, often with laboratory and clinical improvement, could be demonstrated in 80 per cent of patients.

Ebeling *et al.* (173) noted that a pre-operative sulfobromophthalein retention of 10 per cent or less gave protection (98 per cent) against post-operative liver complications, while a low serum albumin (below 3 gm. per cent) was associated with a high rate (66 per cent) of complications. Liver failure postoperatively was twice as common in cirrhosis after portacaval than after splenorenal shunts. Welch and his associates (174) recommend shunting procedures in patients with cirrhosis and varices before they bleed as a prophylactic measure against possible fatal hemorrhage.

Portal Venography

The diagnostic importance of portal venography is receiving more emphasis. Bonte *et al.* (175) describe the technique and mention the danger of splenic rupture with hemorrhage. Ruzicka *et al.* (176) present anatomical and physiological considerations of this procedure with excellent photographs of portagrams taken during venography.

Hepatic Coma

A number of factors may precipitate hepatic coma, including hemorrhage, infection, abdominal paracentesis, surgical procedures, sedation, ammonium-containing resins or substances liberating ammonia (177). In the study of 20 cases of cirrhosis with hepatic coma, however, Foulk *et al.* (177) found that 14 showed evidence of recent parenchymal damage at autopsy. Ammonia has been implicated in the precipitation of liver coma since the pioneer work of Kirk who found that 82 per cent of patients suffering from cirrhosis of the liver had an elevated blood ammonia level, and concluded that this was a result of the shunting of portal venous blood into the systemic circulation. This subject has recently been reviewed extensively, and many clinical determinations have been performed (178 to 181) with varying results. Inconsistencies may, in part, be attributed to differences in methodology and difficulties in measuring ammonia levels accurately. Phear *et al.* (180) performed 350 ammonia determinations in 66 patients, 33 of whom were in hepatic coma, and found that the blood ammonia levels usually correlated with the severity of the neurological disturbance. However, 10 per cent of these patients, including those in coma, demonstrated normal ammonia levels regardless of the degree of neurological involvement. An increase in the plasma ammonia level can exist, moreover, in non-comatose patients, as was demonstrated by Zimmerman & Korn (181), who reported an increased ammonia level in 16 patients with hepatic coma, as well as in non-comatose patients with cirrhosis and hepatitis.

An explanation for the lack of a consistent relationship between blood ammonia and symptoms of coma is presented by Bessman & Bradley (182) who found that muscle tissue removes about 40 per cent of the arterial ammonia, clearing twice as much ammonia from the blood as does the brain. In studying the arterial and venous ammonia levels simultaneously they found that the uptake of ammonia by muscle tissue must be taken into account in the evaluation of blood ammonia levels. Failure, however, to correlate consistently the blood ammonia levels with the signs and symptoms of impending or overt hepatic coma suggests that factors other than the ammonia level itself may be involved (165). The integrity of the intracellular ammonia binding mechanisms may be more important than the plasma ammonia level. Since large oral doses of methionine may precipitate coma, Walshe (183) postulates that disturbances in sulfur metabolism may be important, and agrees that there probably is no single cause to explain all forms of hepatic coma.

Roberts *et al.* (165) discussed the electrolyte disturbances most frequently encountered in patients with ammonia toxicity and found that respiratory alkalosis with an elevated pH and a decreased plasma CO_2 content is a common aberration. Characteristic electroencephalographic patterns in coma were reported by Bickford & Butt (184) although their diagnostic specificity is questionable. Wu *et al.* (185) measured the plasma free amino acids by paper chromatography in 12 patients during hepatic coma. Alanine,

cystine, glutamic acid, glutamine, and tyrosine were all found elevated to varying degrees, but no consistent pattern was observed.

Fetor hepaticus has been responsible for some interesting investigation in the past few years. Challenger & Walshe (186) isolated methyl mercaptan and dimethyl disulfide from the urine of a patient with massive necrosis, and believe that these compounds may be important in the production of this odor.

Treatment.—Many good reviews on the treatment of hepatic coma have been presented recently (187, 188, 189), but specific measures have not been generally successful, and the results are inconclusive, if not discouraging. Improvement with intravenous sodium glutamate, although occasionally promising and dramatic, has usually been absent or transient (190, 191, 192). Larger doses, up to 120 gm. over 36 to 48 hour intervals, have been recommended with some success (190). McDermott and co-authors (191) noted that L-glutamic acid was effective in patients with "exogenous" and "chronic" encephalopathy where ammonia intoxication was the predominant feature, but had little effect in "spontaneous" encephalopathy with true hepatic decompensation. Alexander *et al.* (192), however, found that glutamic acid afforded no greater protection against coma than placebo administration and could not correlate the blood ammonia level with the severity of the coma. The pharmacological and biochemical aspects of glutamine metabolism are reviewed by Meister (193).

Massive doses of cortisone have seldom produced more than temporary benefit in cirrhosis with hepatic coma. However, in coma complicating fulminant hepatitis, large doses of cortisone and ACTH have been followed by recovery in some patients (194). Other therapeutic suggestions include the administration of 5 to 10 per cent CO_2 and oxygen if respiratory alkalosis supervenes, and attention to individual electrolyte problems, particularly those of potassium and phosphorus (165).

Viral Hepatitis

Neefe *et al.* (195) in an extensive follow-up study of a group of veterans who had developed acute viral hepatitis in World War II, found no increased incidence of demonstrable liver disease, and concluded that the development of chronic hepatic disease following acute viral hepatitis may depend on an association of hepatitis with other etiologic or predisposing factors.

A long and carefully controlled study was undertaken by Chalmers *et al.* (196) to evaluate the role of diet, rest, early ambulation, and exercise upon the course of viral hepatitis, and the incidence of relapses and residual disease. Acutely ill patients with infectious hepatitis improved as rapidly when allowed to be up and about the ward at will as did patients kept at strictly enforced bed rest. Patients forced to eat a diet supplying an abundance of calories, proteins and vitamins improved somewhat more rapidly than did those eating only what they chose of a normal diet. In the follow-up study one year after treatment no differences were discernible between the

patients who had been treated with different regimens. However, since this study was performed on a young, healthy group of military personnel during a mild epidemic of hepatitis, it is difficult to generalize on the importance of bed rest in this disease.

Chancey & Zatz (199) reported a series of 43 patients with acute anicteric hepatitis associated with upper respiratory infections. Although hepatomegaly, liver tenderness, and splenomegaly were common findings only a minority of the patients presented any laboratory evidence of liver dysfunction. The epidemiological aspects of hepatitis are discussed. Joske *et al.* (198) reported two patients with active chronic viral hepatitis, one of whom developed the lupus erythematosus syndrome. LE cells were demonstrated in both patients. The use of cortisone in the treatment of infectious hepatitis has not found general favor, although Ducci & Katz (194) demonstrated a shortened symptomatic period, more rapid subjective improvement, and an early fall in bilirubinemia in patients with acute fulminant hepatitis treated with cortisone for a relatively short period of time.

Laboratory studies.—Paper electrophoretic studies in viral hepatitis demonstrated a distorted alpha-2 globulin peak, a slightly enlarged beta globulin peak, and a prominent increase in gamma globulin with a lowered seromucoid value, and a one plus C reactive protein (199). The urinary excretion of amino acids in hepatic necrosis is greatly increased (200). Eder *et al.* (201) demonstrated abnormal lipoproteins in the plasma of patients with early acute hepatitis, obstructive jaundice and biliary cirrhosis utilizing chemical fractionation of the plasma proteins, paper electrophoresis and ultracentrifugation. These abnormal lipoproteins did not appear in portal cirrhosis.

Other Forms of Jaundice

Constitutional hyperbilirubinemia.—Constitutional hyperbilirubinemia (familial non-hemolytic icterus, or constitutional hepatic dysfunction) is a clinical entity to be distinguished from a recently described syndrome termed "chronic idiopathic jaundice with unidentified pigment in liver cells." Blanton & Blanton (202) and Eanet & Brick (203) review the literature on constitutional hyperbilirubinemia and outline the clinical and laboratory criteria for diagnosis. These include: (*a*) fatigability, anorexia, occasional abdominal pain; (*b*) acholuric jaundice; (*c*) absence of hepatomegaly or splenomegaly; (*d*) normal visualization of the gallbladder by x-ray; (*e*) negative liver biopsy; (*f*) mild jaundice with an elevated indirect serum bilirubin; (*g*) completely normal liver function tests, and (*h*) a definite familial tendency, probably a dominant mendelian trait which may be carried by either sex. Steroid therapy has little, if any, effect on the level of serum bilirubin in constitutional hyperbilirubinemia, which may be helpful in distinguishing this syndrome from hepatitis (203).

Chronic idiopathic jaundice.—The essential features (204, 205) of chronic idiopathic jaundice with unidentified pigment include: (*a*) a dark brown or

black appearance of the liver on needle biopsy; (*b*) unidentified coarsely granular lipochrome pigment in the cells of the liver lobule; (*c*) increase in the direct as well as the indirect serum bilirubin; (*d*) abnormal thymol, cephalin flocculation and sulfobromophthalein liver function tests; (*e*) nonvisualization of the gallbladder; (*f*) bilirubin in the urine and (*g*) an enlarged and sometimes tender liver with non-palpable spleen.

Chlorpromazine jaundice.—Chlorpromazine jaundice has been described in many articles. Apparently this drug causes selective injury to the finer biliary radicles with minimal parenchymal involvement, similar to the damage resulting from methyltestosterone and thiouracil (206). There is no direct toxic action on the liver since there is no correlation between dosage and degree of jaundice (207). The incidence of jaundice appears to approximate one per cent, with clinical symptoms varying from pruritis alone to a syndrome of vague abdominal complaints, anorexia, nausea, vomiting, chills, rash, and fever to 102° (208, 209). Liver function tests give evidence of obstructive jaundice with an increase in alkaline phosphatase, hyperbilirubinemia, occasional elevated cholesterol, and usually negative flocculation tests (206, 209). Occasionally peripheral eosinophilia and agranulocytosis (210) are seen. The jaundice may persist for six months, although the mean duration was two weeks (208). Liver biopsy reports differ somewhat, but microscopic sections usually reveal cholestasis with plugging of biliary canaliculi, mild nonspecific infiltration in the lobule, round cell infiltration within the portal triads, and occasional degeneration of some polygonal liver cells (206, 211).

Drug jaundice is also reported with carbarsone (212), sodium para-aminosalicylic acid (213), and phenylbutazone (214), which may be similar to chlorpromazine jaundice and must be differentiated from extrahepatic obstructive disease. In an excellent review of intrahepatic obstructive jaundice Johnson & Doenges (215) suggest that ACTH may be helpful in distinguishing intra from extrahepatic jaundice by inducing a prompt fall in serum bilirubin in the intrahepatic group.

PANCREAS

Physiology

Interesting studies relating to carbonic anhydrase and pancreatic secretion by Dreiling *et al.* (216) indicate that the powerful carbonic anhydrase inhibitor acetazoleamide (Diamox) depresses the total volume and total bicarbonate response of the pancreas to secretin. The basal rates of pancreatic flow and bicarbonate secretion also appear to be inhibited while bicarbonate concentration is unaffected. Sodium, potassium, and the anion concentration of chloride plus bicarbonate are independent of the rate of secretion (217). Dreiling *et al.* conclude that carbonic anhydrase is essential for the secretion of bicarbonate by the human pancreas, and is not concerned with the secretion of amylase. Pancreatic juice in the presence of bile increases cholesterol

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esterification and absorption (218). Although the rate of cholesterol absorption appears to be related to its esterification in the intestinal wall, it is diminished significantly following pancreatectomy.

Fibrocystic disease of the pancreas.—di Sant'Agnese (219) characterizes fibrocystic disease of the pancreas as an hereditary disease of children in which many and perhaps all exocrine glands are involved. A study of 325 cases demonstrated involvement of the liver, sweat glands, salivary glands and lungs, as well as the pancreas. The sweat glands secrete abnormally high concentrations of sodium chloride, which may be of diagnostic significance. Treatment is directed toward dietary measures and control of the respiratory disease with antibiotics. Of 325 patients seen in 15 years, 168 were still living.

Carcinoma of the pancreas.—In a clinical discussion Kaufman & Wilson (220) emphasize the importance of pain as one of the most common presenting symptoms of carcinoma of the pancreas, in contrast to jaundice as the most frequent initial symptom of ampullary cancer. Although no five-year survivals for cancer of the head of the pancreas had been reported prior to 1949, the authors found eight reported five-year survivals after pancreaticoduodenal resection for carcinoma at the head of the pancreas, and 21 reported five-year survivals for ampullary cancer. Survival for the arbitrary period of five years, however, does not necessarily imply a cure. The average survival time for pancreatic head cancer was approximately one year, approaching two years with ampullary cancer. The operative mortality for pancreaticoduodenal resections varied from 11 to 50 per cent.

Bond & Elman (221) in a comprehensive review of the literature on the pancreas include six reported cases of carcinoma of the pancreas in patients under 20 years of age. In their series 18 of 29 patients undergoing radical resection for carcinoma of the head of the pancreas survived; five of these died within five to 15 months, and the remaining 13 were alive for a period up to 56 months after operation. The use of splenoarteriography for detecting space-occupying lesions of the body and tail of the pancreas has been reviewed by Lewitan *et al.* (222).

Pancreatitis.—In a discussion of experimental pancreatitis Grossman (223) reviews a number of divergent approaches to the problem including obstruction of the pancreatic ducts, stimulation of pancreatic secretion by drugs or food, interference with the blood flow to the gland, mechanical and chemical trauma, and the administration of the amino acid ethionine, an analogue and antimetabolite of methionine. In evaluating the significance of these factors in human disease Grossman concludes that in most instances it is not possible to reconstruct the process on this premise. In an interesting symposium on pancreatitis Bockus *et al.* (124) present the clinical features, laboratory findings, roentgen studies and treatment in a series of 78 patients with acute pancreatitis. Similar studies have also been reported by others (225). Specifically considering the management of patients with acute pancreatitis, Jones (226) presents a comprehensive program for supportive, symptomatic and antibiotic therapy.

Alcoholism as a predisposing factor in the development of pancreatitis has long been recognized. In a series of 108 patients with proven pancreatitis at the West Roxbury Veterans Hospital, the incidence of pre-existing alcoholism was 51 per cent, and pre-existing biliary disease 13 per cent (227). Collins & Owens (228), however, reviewed 35 cases of chronic relapsing pancreatitis who presented no evidence of either biliary tract or gastrointestinal disease.

Sphincterotomy in the treatment of recurrent pancreatitis is still a controversial issue. Doubilet & Mulholland (229), pioneers and strong proponents of this procedure, report good results in a majority of patients. They believe that the disease is caused by a physiological dysfunction of the sphincter of Oddi, which in the presence of a common passageway allows bile to enter the pancreatic duct under tension. Sphincterotomy must be accompanied, they believe, by cholecystectomy, whether the gallbladder is normal or not. Surgery, however, does not prevent attacks of acute pancreatitis resulting from ingestion of alcohol or fats, and consequently a fat-free and alcohol-free regime is recommended.

BILIARY TRACT AND GALLBLADDER

Physiology

Fink (230) measured the hepatic bile secretion of a patient with an external biliary fistula and reported a daily output of about 625 ml. The sodium and chloride concentrations in the bile were higher than those of the serum, while the bicarbonate and potassium were in equilibrium with the serum. After the administration of carbonic anhydrase inhibitor, the bile chloride concentration rose, and the bicarbonate concentration fell. Rundle *et al.* (231) observed a reduction in the volume of biliary drainage to approximately one-half after choledochostomy, with a return to control levels after 10 to 12 days. Dilatations of the duct system at operation increased the daily flow of bile.

Hong *et al.* (232) noted in dogs that relaxation of the sphincter of Oddi accompanied the gallbladder contraction induced by duodenal extracts containing cholecystokinin. Atropine and hexamethonium reduce the intrabiliary pressure "by relaxing the duodenal muscle or the sphincter of Oddi."

Acute and chronic cholecystitis.—Bartlett & Quinby (233) reported a mortality of 0.6 per cent in 1280 patients undergoing cholecystectomy for chronic cholecystitis. Carcinoma of the gallbladder was found in 2 per cent, almost exclusively in diseased gallbladders containing stones. In a series of 716 patients with acute cholecystitis the mortality rate without surgery was 4 per cent. Cholecystostomy resulted in a mortality of 13.5 per cent, and cholecystectomy in 1.3 per cent. The mortality from combined cholecystectomy and choledochostomy was 3.9 percent. Stones were found in 43 per cent of the ducts explored.

Post-cholecystectomy syndrome.—Glenn & Johnson (234) emphasize the importance of a persistent cystic duct in the post-cholecystectomy syndrome,

presenting 35 cases. The authors found intravenous cholangiography of considerable value in visualizing the cystic duct.

Cholecystography.—McDonough & Wise (235) evaluate the use of intravenous cholangiography with iodipamide (cholografin) after cholecystectomy. The predictable accuracy of the method was 86 per cent, excluding those patients with sufficient jaundice or liver damage to prevent visualization of the biliary tree. The authors believe that the procedure is a valuable aid in the study of biliary tract disease. No serious reaction to the intravenous administration of 40 cc. of 20 per cent iodipamide was reported.

In a study of the interpretation of the intravenous cholangiogram Wise & O'Brien (236) noted that visualization never occurred when the serum bilirubin was above 4.8 mg. per cent. The authors believe that intravenous cholangiography is not a substitute for oral cholecystography, but should be used when the gallbladder fails to visualize with the oral dye. Partial obstruction of the common duct appeared to be relatively common in the "post-cholecystectomy syndrome." Ducts dilated to a diameter greater than 15 mm. were found to be partially obstructed, and those narrower than 8 mm. were unobstructed. In the intermediate range between 8 and 15 mm. the diameter of the duct was of no value in determining obstruction. The general indications and contraindications for the use of intravenous iodipamide have been evaluated extensively by various authors (237, 238). Reynolds & Fulton (239) presented their experience with iopanoic acid (Telepaque) in 1000 oral cholecystograms. The gallbladder was visualized in 91 per cent. Calculi were seen in 15 per cent of the visualized gallbladders and in 18 per cent of those which did not visualize. The biliary ducts were demonstrable in 58 per cent of patients studied by this method.

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DISEASES OF THE CARDIOVASCULAR SYSTEM (MEDICAL)[1]

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This chapter is based on the work of colleagues[2] who helped me to peruse thousands of articles; it is concerned particularly with certain disorders of childhood and with the causes and prevention of heart disease, but even within this restricted field it is incomplete. The normal infant's cardiovascular system, congenital malformations and heart diseases acquired in early childhood are discussed in Rossi's *Herzkrankheiten im Säuglingsalter* (1). Donzelot & D'Allaines (2) edit an excellent and comprehensive treatise concerned with congenital anomalies, while the staff of the Karolinska Sjukhuset (3) deal authoritatively with the diagnosis of these malformations, and review the literature up to 1954.

Diagnostic Methods

Criteria for recording phonocardiograms have been agreed upon internationally (4), and advice has been given on reproducing heart sounds on tape recorders (5). McGregor *et al.* (6) calibrate heart sound intensity against a standard sound signal (80 decibels at 500 cycles per second), and show that a loud first sound may be the only evidence of mitral stenosis. Finding frequencies between 60 and 110 vibrations per second adequate for detecting mitral murmurs, and between 150 and 250 satisfactory for aortic regurgitant murmurs, Luisada, Richmond & Aravanis (7) recommend these two bands and a stethoscopic recording for routine use. Spectral phonocardiography gives an impression of the intensity as well as the timing of heart sounds and McKusick *et al.* (8) illustrate its usefulness in a study of congenital heart disease.

Arm-to-lung and arm-to-tongue circulation times can be measured simultaneously; Hodas & Cucci (9) obtained two distinct end points with 4 cc. of Intra-sul. Apparatus devised by Falholt & Kaiser (10) measures continuously small concentrations of T 1824 in whole blood and corrects automatically for variations in oxygen saturation. Dye dilution curves have been used to study cardiac function in children [Harned, Crothers & Whittemore (11)], and to measure intracardiac shunts [Callahan, Brandenburg & Swan (12)] or valvular incompetence [Korner & Shillingford (13)]. The method is inaccurate for the first 15 hours of life, but Prec & Cassells (14) estimate that the average cardiac output in neonates is 540 cc. per minute.

Alimurung & Massell (15) define the limits of the normal P-R interval

[1] The survey of literature pertaining to this review was completed in July, 1956.

[2] I am particularly grateful to Miss F. M. L. Parkes and Miss M. P. Russell; and to Drs. R. S. Astley, Mary Bateman, B. D. Bower, I. J. Carré, J. A. Litchfield, M. J. Meynell, J. S. Oldham and O. H. Wolff.

at different ages and rates, the average varying from 0.146 sec. (rate 65) to 0.103 (rate 185) and from 0.114 sec. (1 year), to 0.15 (13 years). Of electrocardiograms taken from 2752 children with congenital heart disease examined by Brink & Neill (16), 10.5 per cent showed left axis deviation (+29° to −90°). When cyanosed the usual cause was tricuspid atresia; less commonly it was because of Eisenmenger's syndrome, single ventricle, a common arterial trunk or atrioventricular canal, situs inversus with levocardia, or an under-developed right ventricle. Without cyanosis it was found in ventricular septal defects, patent ductus arteriosus, coarctation and aortic anomalies. It is impossible to summarize Fraser's & Turner's (17) comprehensive and important survey of electrocardiographic changes in mitral valve disease. Vectorcardiograms distinguish ventricular hypertrophy more accurately than electrocardiograms and Lamb, Grosgurin & Duchosal (18) detail the changes found, whilst Young, Wolff & Chatfield (19) analyze 100 normal vectorcardiograms.

Fleischner & Sagall (20) have studied the x-ray picture in mitral stenosis. With full exercise tolerance, the vessels taper from the right lung hilum; in grade two disability the main branches are dilated, giving the hilum a well defined tail; in grade three disability, because medium arteries are constricted, the lungs are oligemic and there is no tail, but the lateral and lower part of the hilum stands out clearly. By contrast, in left ventricular failure, Short (21) finds the hilar edges clouded and the lung fissures wide.

Angiocardiography is fully discussed in a book by Abrams & Kaplan (22). Rowe, Vlad & Keith (23) describe the methods used at the Hospital for Sick Children, Toronto, and Boesen *et al.* (24) emphasize the advantages of combining catheterization and two directional angiocardiography for the investigation of congenital heart disorders in infants. A machine designed by Rodríguez-Alvarez & Dorbecker (25) simplifies injection of contrast media. Reactions are probably toxic rather than allergic and cannot be predicted by sensitivity tests or a history of allergy [Sandström (26)]. Thirty-one previously unrecorded deaths, occurring in 3,831,850 urograms, are reviewed by Pendergrass *et al.* (27). In 25 cases death was "immediate" and the preceding reaction was respiratory in ten, nervous six, cardiac two, "shock" two, anaphylactic one, and indeterminate in four.

Closure of Ductus Arteriosus

For three hours after birth most normal infants have significantly less oxygen saturation of arterial blood from the foot than the hand, indicating a flow from pulmonary artery to aorta, and Eldridge, Hultgren & Wigmore (28) show that for 15 hours this flow can be increased or re-established by exposure to low oxygen concentration. The pulmonary artery pressure falls and flow through the ductus changes direction soon after ventilation increases vascular conductance in the lungs of the newly born lamb (29). The ductus, which remains partially open for several hours, then supplies much of the pulmonary blood flow, and Dawes, Mott & Widdicombe (30)

believe this to be an advantage until the lungs are fully expanded, since pulmonary blood flow and arterial oxygen saturation decrease if the ductus is occluded. In a classical paper Born *et al.* (31) demonstrate that, even when the lung is not ventilated, the ductus constricts if arterial oxygen saturation is raised. On the other hand, asphyxia also is followed by constriction, although in such circumstances there is no fall of pulmonary artery pressure. Closure of the guinea pig's ductus is delayed by oxygen lack, but not by reduced atmospheric pressure [Record & McKeown (32, 33)].

Incidence of Congenital Malformations

Theories advanced by Spitzer and others to explain congenital heart malformations on an embryological basis have been appraised critically by Mautner (34), and de la Cruz & da Rocha (35) have suggested a new ontogenetic theory, based on modern studies in developmental anatomy. Absence of spleen was associated in 63 cases with malformations in the conotruncus or atrioventricular canal areas; 40 were males and 23 females, and 55 died in the first year [Biörn (36)].

Richards *et al.* (37) followed 6053 infants born of 5964 pregnancies; cardiovascular abnormalities occurred in 50. The incidence of congenital heart disease in stillborn infants was 5.4 per cent and amongst those dying in the neonatal period 10.2 per cent. It was three times as common in premature as in full term liveborn babies. Of babies dying in the first year, 36 per cent had abnormal hearts. Amongst 5017 infants, Richards *et al.* (38) found 71 with murmurs at birth, and the chance that this indicated organic disease was 1:12. In 22 the murmur persisted for three months, one in three having organic disease. A similar study was made by Gyllenswärd (39); 58 of 11,645 consecutive newborn babies had murmurs. Thirty still had a murmur at three months and of these, 27 had congenital malformations; 16 died in the first year.

Conducting System

Complete heart block is reviewed in all its aspects by Penton, Miller & Levine (40). In 18 of their 251 cases the cause was undetermined. These patients tended to be young and the outlook was good. Campbell & Thorne (41) consider the prognosis of congenital heart block good unless a co-existing malformation itself threatens life, and base this opinion on a reassessment of patients first described in 1934. Only one had had Stokes-Adams attacks; one had changed into sinus rhythm; none had a ventricular septal defect. Lev & Lerner (42) examined serial sections from 22 fetal and newborn hearts and five adult hearts but were unable to find any accessory communication between atrium and ventricle, such as Kent had described.

Shunts Causing Pulmonary Vascular Engorgement

Infants with a history of feeding difficulties, respiratory symptoms, a harsh parasternal systolic murmur and pulmonary vascular engorgement,

usually without cyanosis, may have any one of several malformations. Because of advances in surgery it is important to distinguish these from each other, yet this is often difficult. Harned, Crothers & Whittemore (11) studied 240 children with atrial or ventricular septal defects. The former had a tapping apex, no thrill, a widely split second sound, incomplete right bundle branch block and radiologically no left atrial enlargment. Ventricular septal defects were associated with a murmur and thrill, a forceful apex, often a combined ventricular hypertrophy electrocardiographic pattern, and left atrial enlargement; many died in infancy.

Atrial septal defects.—Phonocardiographic analysis enabled Leatham & Gray (43) to show that increased tricuspid flow is responsible for the loud first sound and delayed diastolic murmur, and increased pulmonary artery flow for the midsystolic ejection murmur. Delayed pulmonary valve closure causes the widely split second sound, and other changes may develop as pulmonary artery pressure rises (cf. 8).

Various types of defect are illustrated by Edwards *et al.* (44) in a valuable article. A persistent ostium primum may be difficult to treat surgically because of its close relationship to conducting tissues and atrioventricular valves [Watkins & Gross (45)]. The defect deforms the anterior cusp of the mitral valve, or less commonly the tricuspid valve, and causes incompetence. As Blount, Balchum & Gensini (46) point out, this leads to progressive generalized cardiac enlargement, a soft mitral first sound, increased pulmonary second sound, and a loud systolic murmur conducted beyond the apex. Electrocardiograms show left axis deviation, combined ventricular hypertrophy and sometimes P-R prolongation [Manning & Taussig (47)].

Anomalous drainage of pulmonary veins.—This condition complicates atrial septal defect. Thirteen patients with partially abnormal drainage are described by Hickie, Gimlette & Bacon (48). The right veins were abnormal in 12, and in two the left veins emptied into a left superior vena cava; 10 cases had pulmonary hypertension. The most useful diagnostic measures were cardiac catheterization and dye dilution curves. Gott *et al.* (49) discuss 30 cases of total anomalous return. Electrocardiograms showed right axis deviation. The characteristic figure-of-eight radiological appearance, owing to distension of right, left, or both superior venae cavae, was less common than a "box-like shape" resulting from the almost horizontal left heart border below the aortic knuckle. The right atrium and ventricle were large, the left atrium small. Oxygen saturation in the right atrium equalled or exceeded that of arterial blood. Angiocardiography enabled McAfee (50) to demonstrate the anomaly completely in a third of his cases, and incompletely in another third; the remainder were recognized by catheterization. Angiocardiography disclosed cases not picked up by catheter. Turbulence of blood entering the atrium from the pulmonary veins produces a filling defect [Sepulveda, Lukas & Steinberg (51)], but filling defects occur physiologically in the right atrium and abnormalities may be difficult

to recognize and interpret [Figley *et al.* (52)]. Selective angiocardiography is a helpful diagnostic test [Rowe, Vlad & Keith (23)].

Ventricular septal defects.—Blount, Mueller & McCord (53) correlated electrocardiographic findings and pulmonary artery pressures. When the shunt caused no rise in pressure electrocardiograms were normal; large equiphasic complexes in central chest leads suggested combined ventricular hypertrophy; left ventricular preponderance was associated with large left-to-right shunts with but little rise in pulmonary artery pressure; marked right preponderance indicated pulmonary hypertension and a small shunt.

Eisenmenger's complex.—Brown, Heath & Whitaker (54) point out that "right ventricular hypertrophy is largely responsible for the dextroposition of the aorta in those cases where there is no evidence of abnormal rotation of the great vessels." Large venous *a* waves and a loud, widely split second sound are characteristic. Cyanosis usually develops late even when the aorta arises from the right ventricle; the aortic override may be recognized by angiocardiography or catheterization. Kohout *et al.* (55) regard increased pulmonary vascular resistance as the result of repeated respiratory infection or of a coincidental congenital vascular abnormality, but Espino-Vela & Mata (56) conclude that the change cannot be congenital as the vessels were normal in two cases in which the septal cusp of the tricuspid valve had sealed the ventricular septal defect spontaneously.

Ventricular septal defects complicated by other anomalies.—A defect of the ventricular septum may deform the tricuspid valve and allow oxygenated blood to flow from left ventricle into right atrium [Stahlman *et al.* (57)]. Another uncommon syndrome is described by Becu *et al.* (58). Clinically five babies had large hearts, pulmonary congestion, weak or absent femoral pulses, central systolic and sometimes diastolic murmurs, and electrocardiographic evidence of left ventricular preponderance. All five died in infancy, and at necropsy the pulmonary artery was wide, overriding both ventricles, but without the transposition characteristic of the Taussig-Bing syndrome. The muscular septum was defective anteriorly and, in addition, subaortic stenosis, coarctation and patent ductus arteriosus were present.

Ventricular septal defects which deform the aortic valve, causing aortic regurgitation, produce signs indistinguishable from a patent ductus arteriosus, except that the murmur is lower. Winchell & Bashour (59) report six cases. Electrocardiograms showed right ventricular preponderance in two, left ventricular preponderance in two, and right bundle branch block in two. Oxygenated blood was obtained from the right ventricle. In four similar cases Philipson & Saltzman (60) used retrograde aortography to demonstrate regurgitation into the left ventricle and thence flow into right ventricle and pulmonary artery. A fistula between aorta and pulmonary artery can be differentiated by aortography or by catheterization [D'heer & van Nieuwenhuizen (61), Aubry (62)].

Patent ductus arteriosus.—Powell (63) comments on nine infants with

this condition. The systolic murmur was often loudest at the apex, and five had no diastolic murmur. One hundred and thirty-eight children with a patent ductus are reviewed by Ash & Fischer (64). Of 74 known to be abnormal in the first year, only 24 had a continuous murmur. Five had the apical diastolic rumble which Pinto & Rodbard (65) consider indicative of a large shunt needing operation. This sign was noted in more than half Aitken's (66) cases, and all had a "wide" ductus and severe symptoms. Radiologically the left atrium was often enlarged (67). Although older patients usually had the characteristic Gibson murmur, the diastolic element was truncated or absent in pulmonary hypertension, and catheterization or aortography was then necessary for diagnosis [Campbell (68)]; electrocardiograms in these cases showed right ventricular preponderance. Eight deaths are recorded (69, 70) in children after ligation of a ductus with reversed flow.

Pulmonary stenosis with increased pulmonary blood flow.—A defect associated with the pulmonary stenosis allows left to right shunt. For example Bowers, Swan & Burchell (71) report four patients who had a communication between aorta and pulmonary artery, and sometimes a ventricular septal defect in addition. Callahan, Brandenburg & Swan (12) discuss pulmonary stenosis with septal defects; those with ventricular septal defects had a mean pulmonary artery pressure exceeding that in Fallot's tetralogy or normal controls, and the pressure gradient across the valve was small. Four patients had both atrial and ventricular septal defects. Nadas, Goodale & Craig (72) and Contro & Brostoff (73) describe the condition in childhood. The patients had a fair exercise tolerance, and cyanosis and squatting were unusual. In the light of six cases associated with ventricular septal defects, and three with atrial septal defects, Hubbard & Koszewski (74) emphasize that physical signs depend on the relative importance of the two lesions. Cardiac enlargement was the rule and a middiastolic apical rumble was usual. In cases with a ventricular septal defect, the systolic thrill and murmur were lower than in cases with an atrial septal defect. In those with an atrial septal defect the pulmonary second sound was split, and there might be an early diastolic murmur at the left sternal edge. The electrocardiographic pattern was of right (or combined) ventricular hypertrophy; left ventricular pressure exceeded the right. Rowe, Vlad & Keith (75) describe four infants with all the anatomical features of Fallot's tetralogy but increased pulmonary blood flow. They had a history of bronchitis and were not cyanosed. The hearts tended to be large, and one had a right aortic arch. In addition to the systolic murmur and thrill the second sound was split. Electrocardiographic patterns were of combined ventricular hypertrophy with a normal axis in two; right and left ventricular pressures were the same, and the gradient across the pulmonary valve ranged from 40 to 90 mm. Hg.

Other Congenital Anomalies

Aortic stenosis.—Children with aortic or subaortic stenosis develop the classical picture slowly and may at first present the clinical features, and

electrocardiographic and x-ray characteristics, of a septal defect [Taussig (76)]. Phonocardiography may help early diagnosis; Reinhold, Rudhe & Bonham-Carter (77) describe a loud, often split, apical first sound, an aortic ejection sound, and a tendency for the second sounds to fuse. Gray (78) observes that splitting of the second sound is exaggerated, paradoxically, in expiration. The development of a mid-diastolic apical murmur is ominous, and Marquis & Logan (79) emphasize the serious import of even slight symptoms, the finding of "classical signs" or increasing left ventricular strain in the electrocardiogram. Similar views are held by Baker & Campbell (80) who point to the risk of delay once it has been decided to operate. They consider it dangerous to measure the pressure gradient across the valve except at operation; a gradient exceeding 50 mm. Hg is an indication for valvotomy [Harken & Black (81)].

Coarctation of the aorta.—In ten years at Toronto (82) 90 infants were seen with coarctation and only one-third survived the first 12 months. To reduce this mortality early operation is advised, for 60 per cent of postductal and 89 per cent of preductal cases died of heart failure. Lang & Nadas (83) prefer medical treatment for these infants and, so long as heart failure improves, defer operation until later childhood. This opinion is shared by Engle & Goldberg (84) who diagnosed 21 cases (eight deaths) before the age of six months, and by Whittemore & Fouts (85) who studied 37 babies, of whom 17 died in the first six months. Even severe cases tend to improve spontaneously by the age of a year.

Preductal coarctation may occur with no murmurs and with a good femoral pulse. Electrocardiographic findings vary. Postductal cases may be diagnosed by retrograde aortography, and preductal coarctation by venous angiocardiograms (23, 82).

The combination of aortic coarctation with patent ductus arteriosus is discussed by Cooley *et al.* (86). In seven cases with postductal coarctation the shunt was from aorta to pulmonary artery, and only one had pulmonary hypertension. Four patients with the ductus inserted at the point of coarctation had pulmonary hypertension with high pulmonary vascular resistance; aortic obstruction was slight and the shunt bidirectional. In three patients who had preductal coarctation flow was from pulmonary artery to aorta.

Dextroversion of the heart.—This is contrasted with dextrocardia by Welsh & Felson (87). The apical impulse was diffuse or close to the sternum and the electrocardiogram was normal. Frontal x-rays showed a right-sided heart with an aortic knob on the left and no obvious pulmonary arc or apex. In the right anterior oblique position the appearance was more normal. The right ventricle was to the right, left ventricle anterior, left atrium to the left and right atrium posterior.

Pulmonary stenosis.—An electrode catheter is valuable for distinguishing between infundibular and valvular stenosis [Emslie-Smith, Lowe & Hill (88)]. Silverman *et al.* (89) report 50 cases with intact ventricular septum. Dyspnea and lassitude contrasted with the slight cyanosis. Brock's method of treatment is recommended when an affected infant develops congestive

failure or when, in an older patient, right ventricular pressure exceeds 100 mm. Hg. Relapse after successful valvotomy is thought by Brock (90) to be attributable to secondary infundibular stenosis, and Rodbard & Shaffer (91) suggest that muscular contraction in the infundibular region during early systole increases the degree of stenosis in a proportion of these cases. Poststenotic dilatation of the pulmonary artery is commoner when the narrow section is short; in Robicsek's (92) opinion turbulence and loss of energy damage elastic elements of the vessel wall, but van Buchem's (93) view is that the arterial dilatation and the stenosis are two separate developmental errors occurring at the same embryological age. Callahan, Brandenburg & Swan (94) review ten cases of pulmonary stenosis (six valvular, one infundibular, three combined) complicated by an interatrial communication. Cyanosis dated from birth in eight cases. Radiologically the pulmonary artery was prominent in five. Selective dye dilution curves showed right to left shunts, exceeding 50 per cent of the systemic flow in five. Absence of a pulmonary artery is discussed by Emanuel & Pattinson (95). When the left pulmonary artery was missing an abnormality of the bulbus cordis was usual, commonly Fallot's tetralogy (20 out of 21 cases), with a right-sided aortic arch in 12 cases. When the heart was normal or the bulbus cordis was not involved, the right pulmonary artery was absent in 17 out of 19 cases. Hematogenous brain abscess is liable to develop when a right to left shunt short-circuits the pulmonary capillary filter, and is especially frequent in Fallot's tetralogy. Newton (96) comments that bacterial endocarditis could be excluded in the majority of seven new and 72 previously reported cases.

Pulmonary Arterial Hypertension

Hypoxia increases pulmonary artery pressure in normal people and Cournand and his colleagues (97, 98) have shown this to be caused in part by increased flow, and partly by another factor, not increased pulmonary vascular resistance, but perhaps displacement of blood from systemic to pulmonary circuit. Dammann & Ferencz (99) describe narrowing of the small pulmonary arteries in newborn infants. There was thickening of media and adventitia and, as a result, vascular resistance was temporarily increased. Ordinarily the changes disappeared in a few months. Evidence in support of a system of pulmonary vasocontrol was presented by several speakers at a symposium in Dundee (100, cf. 101, 102), but Lee maintained that vasomotor effects only become apparent when high pressures exist. He pointed out that flow through the lung capillaries is normally pulsatile (103) and he concluded that, in the healthy adult, pulmonary artery pressure depends chiefly on stroke output. Pulmonary blood flow has to be greatly increased (15 l./min./sq. m.) before pulmonary artery pressure rises, and the lesion responsible for increased flow appears to have some effect on pulmonary vascular resistance. For example, taking only cases with a large pulmonary flow, Wood (100) found vascular resistance markedly

raised in 16 per cent of atrial septal defects, 57 per cent ventricular septal defects and 38 per cent of those with patent ductus arteriosus.

Atrial septal defect.—In an important paper Dexter (104) reasons that, when a septal defect is large, the pressure in both atria is equal but that the right ventricle, being more distensible, accepts more blood than the left, and thereby pulmonary flow is increased. When cyanosis occurs it is attributable, not to raised right atrial pressure, but to low right ventricular output which allows better mixing of blood in the common atrium. If the hypoplastic left ventricle fails, its output remains constant, but its diastolic pressure, and consequently the right ventricular filling pressure, rises. Right ventricular failure is attributable to increased flow and to rising vascular resistance, although the latter is rare before the age of 20. Denolin, Hanson & Lequime (105) consider pulmonary hypertension unusual even in adults; when severe it dates from childhood, is badly tolerated and is dangerous to treat surgically. By contrast Goldberg & Downing (106) observed pulmonary hypertension in eight of 14 cases, although only three had increased pulmonary vascular resistance. Pressures fell but did not always reach normal figures after operation.

Ventricular septal defect.—Repair of a ventricular septal defect relieved previously existing pulmonary hypertension [DuShane *et al.* (107)]. In 23 cases Blount, Mueller & McCord (108) found pulmonary hypertension, with high vascular resistance in six, and greatly increased flow and only slightly increased resistance in ten. In their opinion the pulmonary hypertension was not attributable to a congenital vascular defect.

Patent ductus arteriosus.—Vernant *et al.* (109) showed that clamping the ductus immediately reduced pulmonary artery pressure when its mean exceeded 15 mm. Hg, but was insufficient to reverse the shunt, and Anderson & Coles (110) noted similar changes after surgical closure. On the other hand Lequime & Denolin (111) discount the importance of increased flow, multiple embolisms and a neurogenic mechanism, and believe that increased vascular resistance causes this form of pulmonary hypertension. As it is commoner in Mexico than in America or Europe, they suggest that altitude causes persistence of the fetal type of pulmonary blood vessels. In Campbell's (68) 160 cases pulmonary vascular resistance was variable, and pulmonary hypertension did not correlate with increasing age; it often dated from infancy. Nine of 35 infants reported by Bouchard & Cornu (112) had high pulmonary artery pressures. The hypertension is aggravated by respiratory infections and may become irreversible. Heath & Whitaker (113) point out that the degree of hypertension corresponds with the degree of arterial damage and Brewer (114), in a severe case, demonstrated widespread arterial occlusion with arteriovenous communications developing and bypassing the obstruction.

Other causes.—In four cases multiple strictures with post stenotic dilatations were visualized by angiocardiography. The lobar arteries were affected and Arvidsson, Karnell & Möller (115) regard the condition as congenital.

Three cases of essential pulmonary hypertension were thought to be caused by the mechanical effect of repeated emboli (116, cf. 117); all died suddenly after cardiac catheterization. In nine cases Berthrong & Cochran (118) describe a stenosing pulmonary vascular lesion with arteriolar medial hypertrophy, endothelial proliferation and intimal plaques, and with thrombosis and atherosclerosis in the muscular arteries. Commenting on the close relationship between thrombosis and arteriosclerosis, O'Neal & Thomas (119) found that pulmonary arteriosclerosis was commoner in congenital heart lesions with left to right shunts, but in their view neither pulmonary hypertension nor increased blood flow was primarily responsible. Braunstein's (120) six cases with periarteritis nodosa of the pulmonary vessels had pulmonary hypertension.

Diseases of Endocardium and Myocardium

Dimond, Allen & Moriarity (121) discuss endocardial fibro-elastosis. The usual presenting symptoms were pneumonia, with tachycardia, triple rhythm or murmurs and, radiologically, a large heart with prominent left atrium and congested lungs without enlarged vessels, [Abrams (67), St. John & Cope (122)]. If acute, death was rapid with terminal cyanosis; if chronic, exacerbations and remissions might continue for months [Rosahn (123)]. Premature obliteration of the foramen ovale is always complicated by fibro-elastosis of the left ventricle and Gresham (124) considers this an indication that anoxia plays a part in its production; Paul & Robbins (125) have treated the disease by cardiopexy. The myocardium is but little affected, contrasting with East African endomyocardial fibrosis in which fibrous invasion of muscle is severe and endocardial sclerosis may obliterate the ventricular cavity [Davies & Ball (126)].

Gaunt & Lecutier (127) suggest that familial cardiomegaly may be related to Friedreich's disease, but, in two further families, Campbell & Turner-Warwick (128) found no evidence of this. The pathological changes are described and the opinion is expressed that inheritance is as a Mendelian dominant. Heart block, or sinus bradycardia and bundle branch block were common findings. No cause for the enlargement was found. Paulley *et al.* (129) suspect that toxoplasmosis is responsible for some otherwise unexplained examples of cardiomegaly.

Myocardial necrosis occurs if cortisone is given to mice infected with group B type 3 Coxsackie virus (130), and this virus was isolated from infants dying with myocarditis during an epidemic in a maternity home [Javett *et al.* (131)]. In poliomyelitis, circulatory collapse occurred in 28 out of 1359 cases and 22 died. Hildes, Schaburg & Alcock (132) observed that myocarditis was usual in these cases and noted that ten patients developed vasoconstriction and hypertension before their collapse. Van Creveld *et al.* (133) specify the clinical features of infantile interstitial myocarditis, and Gunnar *et al.* (134) deal with the differential diagnosis of primary amyloidosis of the myocardium.

Rheumatic Fever

Criteria for the diagnosis of rheumatic fever have been revised (135) and Besterman (136) has made a careful study of the heart sounds in acute rheumatic carditis. The short middiastolic murmur was easily confused with a loud third sound or with summation gallop. For phonocardiographic analysis murmurs could be accentuated by intravenous phenylephrine. Of two specific antigen-antibody reactions devised by Skillman *et al.* (137), one was positive in 98 per cent of patients with acute rheumatism, in 48 per cent of inactive cases, and negative in all controls. Sheep red cells coated with heat-killed group A β-hemolytic streptococci from cases of rheumatic fever were used as the antigen; the patient's serum provided the antibody. The presence of C-reactive protein (CRP) is not specific for rheumatism (138) and Elster & Wood (139) found no correlation between CRP and the existence of Aschoff bodies in left atrial biopsies. However Tedeschi, Wagner & Pani (140) although satisfied, after assessing 400 biopsy specimens, that histological examination of the appendage represents the heart as a whole, conclude that the Aschoff body is not a reliable index of rheumatic activity.

Sulfadiazine failed to eradicate group A hemolytic streptococci or to prevent rheumatic fever in patients with pharyngitis [Morris *et al.* (141)]. The first attack of rheumatic fever occurred between the ages of 20 and 29 in 124 of 467 definitely established cases, and Biörck (142) states that 25 per cent of these 467 developed valve disease, compared with 11 per cent of 227 less definite cases, and 33 per cent of cases of chorea.

Using the antistreptolysin antibody titer as their criterion, Stollerman *et al.* (143) found that rheumatic activity might persist for more than six months without evidence of re-infection. Relapses occurring within two months of apparent recovery were not caused by reinfection, but after this period re-infection was responsible. The American Heart Association recommends (144) that a child with a streptococcal infection should be given 600,000 units of benzathine-penicillin G by injection, or 250,000 units by mouth thrice daily for 10 days, and if the patient has had rheumatism, sulfonamide or penicillin should be continued daily for life. Markowitz & Hemphill (145) noted four recurrences in 82 rheumatic children on prophylactic oral penicillin, and five recurrences in 64 children on sulfonamide. Reactions occurred in 2.5 and 11 per cent respectively. Phenoxymethyl penicillin may prove useful for prophylactic purposes, although Mohler, Wallin & Dreyfus (146) found that patients could not be relied on to take their tablets, even for short periods.

Pneumonitis is a rare complication of rheumatism. Lustock & Kuzma (147) studied 35 cases. Symptoms of respiratory distress, cough, chest pain, cyanosis, and hemoptysis were disproportionate to the physical signs in the heart. X-ray films showed increased perivascular marking and eventually consolidation which left a clear apex and base [Sutcliffe (148)]. Analysis of 51 cases of pericarditis in childhood showed that 25 were rheumatic, 13 purulent, three tuberculous, four benign and five miscellaneous; Rossi &

Friderich (149) discuss the differential diagnosis and emphasize the seriousness of rheumatic pericarditis. Only two of the 25 children recovered completely and 14 died. Space does not allow any consideration of chronic valve disease.

Mozziconacci & Caramanian (150) consider that cortisone treatment of acute rheumatism is inhibitory only, having little effect on the final condition, but Markowitz & Kuttner (151) believe that, if large doses (200 to 300 mg. daily) are given within three weeks of onset and are continued until the disease has run its course (e.g. 200 mg. for 40 days, 50 mg. for a further 2 to 10 months), the outlook is much improved. Serious but temporary side effects were observed in 11 of the 40 children treated. Prednisone has the advantage that side effects are much less evident [Casolo *et al.* (152)].

Arterial Hypertension

Pickering's excellent book on hypertension (153) summarizes much original work into the causes of essential hypertension and its inheritance. The relationship between chronic pyelonephritis and hypertension is surveyed by Kincaid-Smith (154) who advances the view that vascular lesions with partial renal infarction may be important factors in this connection. Occlusion of a renal artery, characterized by abdominal or lumbar pain, may be followed quickly by hypertension [Poutasse (155)].

Paroxysmal attacks of sweating and headache are features of pheochromocytoma in childhood, but the blood pressure remains constantly high [Robinson & Williams (156)]. Phentolamine (Regitine), starting with an oral dose of 20 mg. six-hourly, gave satisfactory control before operation. In Orgain's (157) opinion phentolamine (5 mg. injected) is the safest and most reliable hypotensive test for pheochromocytoma, and histamine the most useful provocative agent.

After studying 100 cases of essential hypertension for a period of 18 to 34 years, Burgess (158) estimates that the average life expectancy is 2.7 years less than that given in life insurance tables. In patients over 50 the condition was not progressive if the retinae, heart, and kidneys were normal. A prognostic enquiry by Mathisen (159) surveyed 111 men and 179 women whose systolic pressure exceeded 160 mm. Hg, and with a diastolic pressure exceeding 95 before the age of 44. Ten years later 46 men and 52 women were dead, but the mortality was only 8 per cent in 97 cases with a diastolic pressure which fell occasionally below 95 mm., while it was 43 per cent for the remainder.

The Biological Council organized a symposium on hypotensive drugs (160); the most commonly used treatment appears to be with a rauwolfia preparation combined with pentolinium. Mecamylamine (Inversine), a secondary amine with hypotensive properties, is completely absorbed from the bowel (161) but provokes side effects (162). If the diastolic pressure can be kept constantly below 100 mm. Hg for three years, Perry & Schroeder (163) believe that drugs may be reduced or withdrawn. White (164) favors

surgical treatment for young or middle-aged men. He compares with 50 carefully selected controls 50 patients treated by lumbodorsal sympathectomy. After ten years, 48 control patients had died, surviving for an average of 3.7 years, while only 25 of the treated group had died, with an average survival of 6.1 years. The effect of splanchnicectomy is considered by Huntington & Evans (165). A total of 206 patients were reviewed ten and a half years after operation; 48 per cent of those with grade III retinopathy and 33.4 per cent with grade IV changes were still alive.

Atherosclerosis and Coronary Artery Disease

The proceedings of the American Society for the Study of Arteriosclerosis (166) indicate the main paths of research. The importance of a raised serum cholesterol level is demonstrated by Keay, Oliver & Boyd (167) in cases of progeria which have a high cholesterol level and a marked susceptibility to myocardial infarction. A beautifully designed investigation by Brönte-Stewart, Keys & Brock (168) showed a statistically significant relationship between death rate from coronary heart disease, mean serum cholesterol level and the proportion of calories derived from total dietary fat. Later Brönte-Stewart and his colleagues (169) showed that animal fats or hydrogenated vegetable fats, all rich in saturated fatty acids, raised serum cholesterol especially in β-lipoprotein, whereas comparable amounts of natural vegetable oils, fish, or marine oils had no such effect. Highly unsaturated fatty acids obtained from pilchards or sunflower seeds depressed serum cholesterol even when pure cholesterol or animal fats were added to the diet. Phenylethyl acetic acid also reduced serum cholesterol (170) and so too did triiodothyroacetic and tetraiodothyroacetic acids (171, 172).

A stimulating correspondence was provoked by Sinclair's letter (173) suggesting that atherosclerosis may be a deficiency disease, since food "improvers" and hydrogenated fats cause an inadequate intake of essential fatty acids, such as linoleic and arachidonic acids, which are needed more by men than women. Because such diets also contain a high proportion of saturated and unnatural fats, cholesterol is esterified with abnormal fatty acids.

The diet and habits of Navajo Indians are like those of people living in Cleveland, yet the former have less coronary disease and lower cholesterol levels, and Page, Lewis & Gilbert (174) suggest that this is hereditary. Similarly, according to Lee & Thomas (175), the incidence of coronary disease is greater amongst the white than amongst the negro population in America and, because the incidence has increased more rapidly in women than in men during recent years, the sex ratio is changing. In the white population Keil & McVay (176) calculate that coronary artery disease is commoner in men than women in a ratio of 2.9:1, whereas they found a ratio of 1.2:1 amongst Negroes. Furthermore first attacks of coronary thrombosis affect Negro women at an average age of 56, 10 years earlier than white women.

James, Post & Smith (177), reviewing the records of 146 white women, observed that only 11 were still menstruating when infarction occurred, and all but one of these had either diabetes mellitus or hypertension. Evidence collected by Peel (178) leads him to conclude that estrogenic hormones are not protective, but rather that men are abnormally susceptible while women show the incidence expected in a disease due to ageing. Ten per cent of young American soldiers killed in Korea had coronary arteries seriously narrowed by atheroma, while Japanese soldiers were not affected (179). If, therefore, a modified diet is necessary to prevent atherosclerosis it must be started early; indeed Pomeranze (180) finds that cow's milk raises serum cholesterol more than soy milk and implies the possibility that "the atherogenic tendency is initiated in infancy."

Although atherosclerosis is important, life's chapter is often closed by intravascular thrombosis, and this too is influenced by diet. O'Brien (181) has shown that a fatty meal accelerates blood coagulation. This may be due to the chylomicra of ethanolomine phosphate [Robinson & Poole (182)] or to a closely related group of phospholipides occurring almost exclusively in milk products [Maclagan & Billimoria (183)]. In Duguid's (184) opinion, atherosclerosis is itself a result of intravascular clotting and this view receives support from electronmicroscopy [Levene (185); cf. 119)]. Ventricular fibrillation is readily initiated when part of the myocardium is well oxygenated and an adjacent area anoxic, and Brofman, Leighninger & Beck (186) have demonstrated that the oxygen differential is also responsible for the RS-T elevation.

The value of various anticoagulants was discussed at the first International Congress on Thrombosis and Embolism (187), and modern practice in the treatment of coronary thrombosis is reviewed by de Francisco & Wright (188) and Gilchrist & Tulloch (189). Prolonged after-treatment with anticoagulants has been advocated by Suzman, Ruskin & Goldberg (190), amongst others, and Engelberg, Kuhn & Steinman (191) claim a significant prognostic improvement when as little as 200 mg. heparin is injected subcutaneously twice a week.

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DISEASES OF THE CARDIOVASCULAR SYSTEM (SURGICAL)[1]

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Preconceived ideas are like searchlights which illuminate the path of the experimenter and serve him as a guide to interrogate nature. They become a danger only if he transforms them into fixed ideas—this is why I should like to see these profound words inscribed on the threshold of all the temples of science. The greatest derangement of the mind is to believe in something because one wishes it to be so. . . .

Louis Pasteur

The authors cannot conceive of any more succinct way of stating the objectives of this review upon the accomplishments of cardiovascular surgery than to quote these discerning words of Pasteur. Imagination is needed to give wings to thought at the beginning of experimental investigations on any given subject. When, however, the time has come to conclude and to interpret the facts derived from observation, imagination must submit to the factual results of the experiments.

In this paper we have reviewed certain papers in more detail than others for one or more of the following reasons: (*a*), the paper represents a milestone in the subject; or (*b*), the conclusions of the author(s) have been widely quoted without general realization of the strength or the weakness of their evidence; or (*c*), the data or the conclusions of the authors are subject to an alternative interpretation which is worthy of the reader's attention.

For the sake of clarity we have included a summary at the end of each of the major sections, and, believing that bold speculation is the lifeblood of progress, we have not been averse to predicting the likely trends of future development in this energetic field as we see them.

Direct Vision Intracardiac Surgery

Although the past decade has brought forth an impressive display of clinical achievements in the field of cardiac surgery it was equally apparent that save for a few notable exceptions these accomplishments were confined to anomalies and disorders which are situated outside the chambers of the heart. In effect, the interior of the heart represented the last anatomic frontier confronting surgeons.

The present great advance in cardiac surgery has been the development of the open operation in which the surgeon sees precisely what has to be done, and then proceeds to do it under direct vision. The surgical correction of many intracardiac lesions, not previously amenable to curative procedures, has required the development of these safe and effective methods which are

[1] This review covers the period since the last review and was concluded November, 1956.

now available and in daily use for working within the chambers of the open heart.

General hypothermia.—Historically, this was the first method to allow successful intracardiac reparative surgery [closure of an atrial septal defect (1)] under direct vision as a routine procedure in man. In further experimental studies to extend the application of this method, Niazi & Lewis (2) have produced profound hypothermia in dogs. The temperature was brought below 10°C. Ventricular fibrillation was prevented by giving 10 per cent carbon dioxide. Carbon dioxide prevented the fall in pH, but in this group death of the dog occurred during rewarming. Cardiac standstill occurred by giving 5 per cent carbon dioxide while the temperature of the dog was lowered to 20°C. and then 100 per cent oxygen between temperatures of 20° and 10°C. This method resulted in a good survival rate during rewarming. If, on the other hand, the heart continued to beat at low temperatures rewarming carried a high mortality. Cardiac arrest by this method has been maintained for 60 to 75 min. They concluded that the shift of pH to the alkaline side below 20°C. was the important factor in preventing ventricular fibrillation.

Shumway & Lewis (3) induced fibrillation electrically during hypothermia by using a fibrillating current of 0.25 amps at 12 v. for 0.5 seconds. Defibrillation was accomplished by using a current of 1.5 to 3 amps. at 120 v. for 0.1 sec. Prior to defibrillation epinephrine was injected into the heart and vigorous cardiac massage was instituted until the myocardium became pink. Peddie, Creech & Halpert (4) have summarized the severe and frequently fatal structural changes observed in the hearts of patients subjected to cardiac massage.

Riberi *et al.* (5) studied the effect upon ventricular fibrillation of infiltration of the sino-auricular node. Dogs were cooled to 30°C. Inflow stasis for 10 to 12 minutes either produced fibrillation or this occurred when the superior vena cava was released. When the sino-auricular node was infiltrated with 1 per cent procaine until the P wave in the ECG was abolished, ventricular fibrillation was prevented in all cases. However, an important deterrent to the use of the method clinically, in the opinion of the reviewers, is the fact that the infiltration of any liquid into the heart muscle is likely to result in damage due to disruption of muscle fibers and hematoma formation.

The effect of sympathectomy on ventricular fibrillation was studied by Shumacker *et al.* (6). Dogs in which a bilateral dorsolumbar sympathectomy had been performed showed a very low incidence of this common complication of hypothermia. Stimulation of the right vagus nerve also protected against ventricular fibrillation in 83 per cent of the animals. Trimethaphan camphorsulfonate (Arfonad) given intravenously resulted in protection of 87 per cent and, paradoxically, section of the vagus, distal to the origin of its cardiac branches, gave protection in 80 per cent. Covino & Hegnauer (7) found that a combination of controlled respiration (to maintain blood pH

near normal) and intravenous administration of a procaine derivative reduced the incidence of ventricular fibrillation in hypothermic dogs.

McMurrey *et al.* (8) correlated EEG changes with periods of cerebral vascular occlusion during hypothermia. Electrical activity ceased after one minute of occlusion, irrespective of the temperature. Fifteen minutes of occlusion was well tolerated at 23° to 26°C. Multiple periods of 12 min. each were also tolerated, provided there was an adequate rest period between each period of occlusion. Slow return of EEG activity indicated cerebral damage. Activity persisted longest in the parietal and frontal areas of the brain. The same investigators (9) used the EEG to maintain the level of anesthesia constant during hypothermia in monkeys. They demonstrated that there was a decrease in cerebral vascular flow with increase in cerebral vascular resistance which was independent of the tension of carbon dioxide and of oxygen. The assumption was that the increase in resistance was due to spasm and increased viscosity of the blood. The oxygen consumption of the brain at 26°C. was 25 to 30 per cent of normal. Glucose metabolism was also diminished. They concluded that the anerobic processes were also slowed in the brain, as the brain will tolerate vascular occlusion five times as long at 26°C. as at normal temperatures, although oxygen consumption is decreased by only one-third to one-fourth. Finally they concluded that the maximum benefit from hypothermia was obtained at temperatures from 28° to 29°C. Below this level the risk of cardiac arrhythmia was great.

Stone *et al.* (10) confirmed the increase in vascular resistance of the cerebral circulation and the decrease in metabolism in three human volunteers. They also showed that shivering caused a rise of 100 per cent in the oxygen consumption even at hypothermic temperatures. Marshall *et al.* (11) have shown experimentally that the safe period of cerebral vascular occlusion was reduced from 12 to 8 min. if the veins were also occluded. They considered that clinically 12 min. is the upper limit of safety for vascular occlusion during hypothermia. Subsequently, Swan & Blount have shortened the recommended period for safe circulatory occlusion to 8 min. (12).

Baer *et al.* (13) investigated the protection against ventricular fibrillation during hypothermia afforded by coronary injection of neostigmine when the coronary ostia were patent or occluded. The protective action of neostigmine depends in part on the production of acetylcholine. Production of acetylcholine in turn depends on the concentration of ATP and the latter is mainly produced by the breakdown of glucose. Aerobic glycolysis produces 15 times as much ATP as the anerobic process. When the coronary ostia were occluded the protective action of neostigmine was less. Bethanechol chloride (carbamylmethylcholine chloride), which is not affected by cholinesterase, was equally effective under both conditions.

Potassium chloride asystole during hypothermia has been studied by Mavor *et al.* (14). During hypothermia and also during ventricular fibrillation potassium leaves the muscle cells. Asystole was achieved at 26°C., using an average of 7.9 cc. of a solution of KCl (1 m.eq./cc.) at pH 5.6. Restoration

of normal rhythm was accelerated by giving 50 per cent glucose intravenously together with insulin.

It is interesting that hypothermia per se does not provoke a stress response as measured by the 17-hydroxy-corticoid concentration in the adrenal vein (15). Moreover, the stress response measured in this way, produced by surgery or the injection of ACTH, was diminished by hypothermia.

Lewis *et al.* (16) have used hypothermia for the correction of a case of total anomalous pulmonary venous drainage. The entry of the pulmonary veins was transplanted successfully into the foramen ovale which had been enlarged. Their second case was one of triatrial heart in which a large communication between the third abnormal chamber and the left atrium was made. The abnormal chamber received all the pulmonary veins. These workers state the case for using direct vision and general body hypothermia for intracardiac surgery as the technique is simple and requires relatively simple equipment. Scannell & Brewster (17) record the successful removal of a myxoma of the left atrium under hypothermia.

Summary and conclusions.—The use of general hypothermia as an adjunct to open cardiac surgery has been very valuable. Notable successes have been obtained. However, its usage has been limited owing to the high incidence of ventricular fibrillation and other arrhythmias in the hypothermic heart, and also owing to the irrevocable time limitations imposed upon the surgeon. To this extent the surgeon has remained at the mercy of the pathologic changes. For these reasons it is likely that general hypothermia for open heart surgery will be superseded by the now generally available perfusion systems at normal body temperature.

Pump oxygenators.—During the period covered by this review, there has been rapidly increasing interest in the accomplishments made possible by the utilization of pump oxygenators which allow total cardiorespiratory bypass for the correction of abnormalities of the heart and great vessels. These pump oxygenators have been used almost entirely at normal body temperatures. Their basic structure consists of a venous pump, an oxygenator, and an arterial pump. In some, the venous pump has been eliminated and gravity feed is used (18). In other systems (19, 20) utilized only experimentally to date, the arterial pumping action is produced by rhythmic, manual compression of plastic bags, thus eliminating all mechanical pumps. Oxygenation is achieved by manual agitation of venous blood in plastic bags filled with oxygen in this system.

In others (21, 173, 174) there is an additional mechanical pump, or level sensing devices, which automatically maintains the volume of blood in the extracorporeal circuit at a constant level. One obvious disadvantage of such automatic sensing devices, in the opinion of the reviewers however, is the fact that if the perfusion to and from the patient is proceeding smoothly and in balance, these electronic-servo mechanisms which balance output and input are superfluous; whereas, if for one reason or another an im-

balance develops due to a reduction in venous return (which is the most frequent type of imbalance), these automatic controls function to keep the machine's volume of blood constant at the expense of the patient's blood volume unless they are manually overruled by the human monitor which again makes their presence superfluous.

For the relatively short intervals required, simple mechanical pumps of several types are capable of substituting effectively for this function of the heart. In the past the obstacles to success in this field have been related to the apparent intricacies of rapid oxygenation of relatively large quantities of venous blood outside the body. Two basic systems of extracorporeal oxygenation have proved successful in clinical application. In the one group are the biological oxygenator systems employing cross-circulation, heterologous (dog) lungs, or a reservoir of oxygenated blood. The University of Minnesota group has reported on the results of its use of controlled cross-circulation in patients (22, 23, 24, 25), the use of an arterialized reservoir for repair of ventricular septal defects (26, 27), and the use of an heterologous (dog lung) oxygenator (28, 29) for repair of ventricular septal defects. Mustard & Chute (30) have described their experiences with the monkey's lung used as a clinical oxygenator.

In the other group are the artificial oxygenators employing one of three basic methods for extracorporeal arterialization of venous blood. These are: (*a*), bubble oxygenation in which oxygen in introducted directly into the venous blood; (*b*), film oxygenators in which the red cells are also exposed directly to oxygen by being spread in thin layers over a large surface; (*c*), membrane oxygenators in which oxygen and venous blood are exposed over a large surface separated by a suitable membrane, such as cellulose, which is permeable to oxygen and carbon dioxide. There is now an impressive number of patients who have had direct vision intracardiac surgery with total bypass of the heart and lungs, utilizing one of these methods of extracorporeal oxygenation.

Bubble oxygenator.—A simple disposable artificial oxygenator has been developed and utilized extensively by the University of Minnesota group (31, 32). DeWall *et al.* (33, 175) have reported upon the physiologic responses in the first 120 patients undergoing total body perfusion utilizing this oxygenator. The mean arterial pH values at the end of the bypass period for all 84 of the acyanotic patients (the flow rate utilized varied from 30 to 55 cc./kg. body weight/min.) were all within the normal range (7.40 to 7.45). Thus there was no acidosis, and no base was administered to these patients during their perfusions. In the 31 cyanotic patients, the postperfusion arterial pH value remained at the preperfusion control levels. A depression of the patient's plasma bicarbonate levels after total body perfusion was observed in all cases and this was not significantly greater than the normal daily variation. Serum potassium levels were observed to decline during perfusion and to return to normal levels within two hours. This alteration in serum potassium correlated with, and was believed to be

a result of, the observed elevations in the blood glucose levels. Postperfusion plasma hemoglobin values for the first 50 patients varied from 6 to 75 mg. per cent with a mean value of 30 mg. per cent. Maximum metabolic efficiency is obtained by the bubble type oxygenators because of the fact that the blood is filmed directly upon the surface of the oxygen globule, thus allowing very great surface areas for the free interchange of gases without the intervention of a foreign material.

Film oxygenators.—Kirklin *et al.* (34) have reported on similar metabolic data for 40 patients undergoing total body perfusion with the Gibbon oxygenator. The perfusion flows varied from 20 to 200 cc./kg. body weight/min. and the postperfusion arterial blood pH values for the various flow rates varied from 7.27 to 7.34 indicating the presence of a degree of uncompensated acidosis, even though sodium bicarbonate was added during the perfusion in 19 patients. In 38 of the 40 patients plasma hemoglobin levels were below 40 mg. per cent. The other two patients had very high levels of 800 and 1500 mg. per cent respectively, believed to have resulted from transfusion reactions.

Kay *et al.* (35), utilizing another type (spinning disk) of film oxygenator, have reported metabolic data for 17 patients undergoing total body perfusion for reparative cardiac surgery. In these patients the flow rates varied from 40 to 80 cc./kg. body weight/min. and the postperfusion arterial blood pH values varied from 7.21 to 7.54 with a mean value of 7.30. Plasma hemoglobin levels varied in this series of patients from 34 to 116 mg. per cent with the higher values occurring in the patients with higher flow rates.

Kolff & Effler (36) have reported upon the develpment and clinical use of a membrane type oxygenator. The advantage claimed for this type of oxygenator is the complete freedom from air embolism. However, this is perhaps nullified by the fact that air embolism has not been much of a problem in perfusion type cardiac surgery. The disadvantages of the membrane type oxygenators (37) in their present state of development are the large priming volumes necessary, the high pressures often necessary to force the blood through the tubing, the tendency of these thin membranes to leak, and the low efficiency of interchange of oxygen and carbon dioxide attributable to the obstruction created by the membrane.

Pump oxygenator plus hypothermia.—From time to time suggestions (21) are made for combining these two methods for open heart surgery. However, this combination is injudicious, based upon physiologic, experimental, and clinical evidence, in the reviewer's estimation. Combining two methods which may be satisfactory or even good in themselves does not necessarily result in a single excellent method. Quite the contrary is the result. The principal limitations of hypothermia are the lowering of efficiency of the myocardium and the increased susceptibility engendered to serious arrhythmias, such as ventricular fibrillation or complete atrioventricular dissociation. The addition of a pump oxygenator to the system in no way lessens these complica-

tions. Moreover, the hypothermia, in turn, lessens the efficiency of any pump oxygenator by the effect of lowered temperature in slowing the physical processes of oxygenation and carbon dioxide removal. Thus, the theoretical gains often cited for this combination, i.e., of being able to perfuse at lower flow rates, is nullified immediately

Control of blood loss from the open heart.—All pump oxygenators in clinical use incorporate some method for returning to the extracorporeal systems blood aspirated from the open heart. This blood is derived from the coronary flow, regurgitation due to displacement or incompetency of the aortic valve and the bronchial collateral system. The latter tends to be very well developed in cyanotic patients. The essence of these systems is to prevent excessive hemolysis by aspirating this blood at a relatively low pressure (under 30 mm. Hg). Donald *et al.* (38) have described their system in detail.

Melrose *et al.* (39) have developed a technique for producing elective cardiac asystole during the bypass period by the administration of potassium citrate into the coronary arteries after cross-clamping the ascending aorta to reduce these blood losses. Arrest is thought to be beneficial, as oxygen consumption by the heart is considerably reduced and presumably then it is in a better position to tolerate the interval without coronary blood flow. The surgeon also has the advantage of better exposure in working upon a still organ. However, there are no measurements of the magnitude of this reduction in oxygen consumption. Since the myocardium needs some oxygen, there are potential drawbacks to the routine use of this method in patients with a low cardiac reserve, and possibly in patients with cyanotic heart disease. Another serious deterrent to routine clinical use of potassium arrest is the fact that the stitch or stitches producing a complete block remain undetected until the heart is closed, at which time it is too late to do anything about removal. Cross-clamping of the aorta does reduce the blood loss into the operative field from the first two sources enumerated above, but does not affect the losses due to the third. The reversibility of potassium asystole has been confirmed experimentally by Kolff *et al.* (40); they have used it clinically in eleven patients with six successes and five deaths (41, 42).

Gott *et al.* (43) have found that elective potassium asystole, in dogs for 15 to 30 min., was not satisfactorily reversed experimentally and 90 per cent of the animals died. The reviewers have preferred to minimize the cardiotomy blood loss, where necessary, by intermittent occlusion of the aorta (44). If it becomes necessary to cross-clamp the ascending aorta and thus deprive the heart of coronary flow for any length of time, then it is advisable to support the beating myocardium by retrograde perfusion of the coronary sinus with oxygenated blood (45, 46). In selected patients where adequate surgical exposure has been difficult, the reviewers have found elective potassium asystole to be a valuable addition to the armamentarium of the cardiotomist.

Summary and conclusions.—The mechanical oxygenator has taken its place in surgery. The interior of the human heart no longer constitutes an anatomic barrier to surgeons. Both of the two types of artificial oxygenators which have had the most extensive clinical application to date, namely the film and the bubble oxygenators, appear to offer reproducible and reliable methods for temporarily supplanting the functions of the human lung. The bubble oxygenator, because of its simplicity and greater metabolic efficiency, would appear to offer advantages in regard to wide applicability. Obviously, time will be the final arbiter. The membrane oxygenator, while workable, has some serious limitations in terms of efficiency and unless these can be overcome it is doubtful if it will find wide application.

The availability of effective pump oxygenators for working within the open heart of man is changing the research emphasis in this field. From the development of methods for open cardiotomy exploration is shifting toward development of surgical techniques which permit the application of the benefits obtainable by open cardiotomy to an ever-increasing variety of congenital cardiac malformations and acquired diseases of the heart, not curable by existing methods.

Atrial Septal Defects

Preferential flows in experimentally produced defects have been studied by use of the dye dilution method (47). Blood from the inferior vena cava was found to shunt through the defect in a right to left manner. This finding applies to a much lesser extent to blood from the superior vena cava. Dye injected into the right pulmonary artery was found to shunt from left to right to a greater extent than dye injected into the left pulmonary artery. This may indicate that blood from the right lung is functionally more important in the left to right shunt than that from the left lung. Clinically it is worthwhile to distinguish between functional and anatomical anomalous pulmonary venous return. The cause of this preferential shunting is probably largely anatomical, as the opening of the inferior vena cava lies close to the defect and the entry of the right pulmonary veins is also close to the septum. Complete mixing of blood in both atria does not occur before the blood leaves either collecting chamber.

Downing & Goldberg (48) have analyzed the findings in 100 patients with atrial septal defects of secundum type. Seventy-two patients were females and in 34 the diagnosis of heart disease was first made after the age of ten years. In 65 the pulmonary artery pressure was raised and in eight it equalled the systemic pressure. At lower pressures the shunt was quantitatively greater and the basic considerations for operation are, in their opinion, the size of the shunt and the level of the pulmonary artery pressure. Usually, the shunts in atrial septal defects are greater than in ventricular septal defects. Longmire *et al.* (49) have analyzed 34 cases and have come to similar conclusions. Kirklin & Ellis (50) state that cases with a left to right shunt of

50 per cent or more should be operated on, even if they are symptom free

A number of surgical methods for the closure of atrial septal defects are currently in use. Basically these may be arranged into two main subdivisions: (*a*), open direct vision as advocated by Lewis, Swan, these reviewers, and others; and (*b*) blind as utilized by Gross, Kirklin, Sondergaard, Bailey, and others.

In the treatment of atrial septal defects clearly the therapeutic goal is a curative result and the results of treatment need to be evaluated by postoperative physiologic studies preferably done several months or longer after operation. Low mortality in itself, while obviously important, is meaningless in evaluating whether the patient has been cured, because most patients with atrial secundum defects, unlike ventricular septal defects, will survive a thoracotomy and exploratory cardiotomy even though their defect may not have been completely closed, nor even closed at all.

Lewis (51) has operated upon 61 patients with ostium secundum or ostium primum defects under general body hypothermia for direct vision repair with six deaths (10 per cent). Twenty-nine of these patients have been studied by postoperative catheterization with objective cure proved in 27 and a shunt remaining in two patients. Swan & Blount (12), utilizing a similar method, report operations in 60 patients with 11 deaths (18 per cent). Twenty-seven of their patients have been recatheterized with a residual shunt remaining in only two.

Kirklin has continued to advocate the Gross well technique and reports a very low mortality in 71 patients [three deaths, 4 per cent (52)], but in those patients studied postoperatively (53) at some interval after operation there was a higher incidence of detectable residual shunts, although in some instances these residual defects apparently were small in size as most of the patients were deemed to have had good clinical imporvement.

On the other hand Husfeldt (54) reports four deaths in 16 patients operated upon by the closed method of Sondergaard. Of the 12 survivors 9 were recatheterized and in none was the defect closed. Husfeldt felt that these poor results were due to a pulling out of the stitches tied under tension when the heart was distended and pumping blood.

Summary and conclusion.—While at present there is no unanimity of opinion as to the method of choice for surgical treatment of atrial septal defects, a variety of methods is available; it is safe to assume that the trend is and will continue towards more widespread application of direct vision open methods for repair since a higher percentage of cured patients may be anticipated. The results of the touch methods have been acceptable and even good in selected patients in the past. For the future, however, it is unlikely that they will remain acceptable to the majority of surgeons and cardiologists inasmuch as the accuracy and scope of visual surgery opens up far wider fields of endeavor and accomplishment in terms of better results for a greater number of patients.

Of the open methods, use of the pump oxygenator will doubtless supersede general hypothermia since the operative risk appears less because of fewer serious arrhythmias, and more time is available; there is also freedom to deal definitively with associated defects including ostium primum and atrioventricularis communis defects. It may be emphasized that it is not possible to deal curatively with the atrioventricularis communis defect by closed or blind methods because in addition to repairing the complex septal defect(s) the regurgitation, mitral, tricuspid (or both), must be managed by careful suture of the cleft valve leaflet(s); nor is it possible to manage this defect curatively by hypothermia because of the insufficient time available; a perfusion system is essential. The use of a pump oxygenator perfusion system for all patients undergoing reparative surgery for atrial septal defects has effectively solved for the cardiologist and surgeon the difficult problem of accurately differentiating preoperatively in all instances an ostium primum defect from a secondum lesion.

Ventricular Septal Defects

In the past there has been little question of the desirability of closing ventricular septal defects, particularly those associated with pulmonary hypertension (which includes the vast majority). Moreover, ventricular septal defect is a common congential cardiac malformation (55). It probably ranks second only to patent ductus arteriosus in incidence. Of all patients born with a ventricular septal defect, in the days prior to corrective surgery, 95 per cent or more died of their defect; it is of interest that 50 per cent of these patients died in their first year of life (56, 57). Of those surviving this hazardous initial twelve months very few have reached their teens. In the reviewers' experience most of the older patients, some of whom have been carried in the clinical records for years as ventricular septal defects or Eisenmenger's complex, have been found upon surgical exploration to have some variant such as truncus arteriosus communis, "corrected" transposition of the great vessels, or one of the forms of single ventricle with or without complete transposition of the great vessels. The finding of an isolated ventricular septal defect in these older patients, while it does occur, has been unusual. Thus, the conclusion is inescapable that few patients born with an isolated ventricular septal defect survive beyond the pediatric age group without corrective management.

The lethal element of ventricular septal defects is, primarily, the early rapid, and progressive development of pulmonary hypertension associated with pulmonary vascular pathologic changes. The potent stimulus to these arteriolar alterations in the lungs associated with ventricular defects is not the increased blood flow through the lungs (patients with atrial ostium secundum type defects as a group have left to right shunts of a far greater magnitude than do those with ventricular defects, but the onset of pulmonary hypertension is late) but rather the fact that the pulmonary vascula-

ture is exposed freely to the systemic resistance and each systolic thrust of the left ventricle is imparted undamped to the lung vessels through the defect.

Anatomy and physiology.—The availability of surgical treatment for ventricular septal defects has stimulated a renewed interest in their pathophysiology. The location of ventricular defects in 100 autopsied patients has been analyzed by Downing & Goldberg (58) who conclude that the defects in the membranous area, which also occurred most commonly, were malformations of serious import. They found defects in the muscular portion of the septum to be rare and thought that some of these evidently closed during ventricular systole so that shunting was minimized. Becu *et al.* (56) carried out an excellent study on 50 autopsy cases with ventricular defects. Sixteen or 32 per cent of their patients had other associated cardiovascular malformations as well. Also, of these 50 patients, 27, or more than half, were considered to have died of their ventricular defect in the first 12 months of life; this emphasizes once again the lethal nature of many of these defects.

Warden *et al.* (59), in a surgical-pathologic classification of ventricular septal defects based upon observations made during repair on 120 patients, found that Rokitansky's (60) anatomical classification, together with the embryologic observations of Spitzer (61), were the most valuable in recognition and categorization of the various types of ventricular septal defects. In this series of patients, selected for surgical treatment because of evidences of physical deterioration, the pars membranacea defect was also the preponderant finding. However, although less frequent, defects in the anterior or posterior muscular septa usually were also associated with severe hemodynamic effects. While there has been some correlation between the size of the ventricular defect and the degree of clinical disability in patients with isolated ventricular defects, there has been a tendency to overemphasize this point in explaining disability. This is understandable because nearly all such studies have been on autopsy material. These authors suggest that a factor at least as important in determining the patient's degree of disability has been the precise anatomical relationship of the defect to the orifice of the pulmonary artery. In these defects associated with the severest changes, the systolic bolus of blood from the left ventricle enters the pulmonary artery directly, whereas in certain other defects of equivalent size the systolic jet of blood from the left ventricle strikes the opposite wall of the right ventricle; the turbulence thereby created produces a functional pulmonic stenosis serving to protect the lungs to a degree. The frequency and importance of recognizing associated defects in patients operated upon with a diagnosis of isolated ventricular defect have been emphasized by these authors. Almost 30 per cent of patients believed, preoperatively, to have an isolated ventricular septal defect had associated lesions such as atrial defects, patent ductus arteriosus, coarctation of aorta, mitral stenosis, left superior vena cava, "corrected" transposition, or multiple defects in the ventricular septum.

Surgical treatment.—Experimentally produced ventricular defects have been closed by blind methods (62). Clinical success has not been reported with such closed methods for ventricular defects. The first patients with this defect to have closure were managed by open cardiotomy and an extracorporeal circulation utilizing controlled cross-circulation. In the first eight patients (22) there were six survivors and recatheterization was carried out in four with complete closure in all instances. In the total series managed by cross-circulation there were 27 patients operated upon with 19 survivors (24). Subsequently, 53 patients with ventricular septal defects have had surgical closure utilizing a pump oxygenator; 13 deaths resulted (63). Kirklin *et al.* (34) have reported closure of ventricular septal defects in 21 patients (17 survivors). Effler & Kolff (41), as already mentioned in connection with potassium arrest, have reported closure in three patients with one death. A more recent report of their results mentions 11 operations with five deaths (42). Campbell *et al.* (28) have reported on five patients with ventricular septal defects undergoing closure procedures utilizing the heterologous lung oxygenator (four deaths). Muller & Dammann (64) have reported the results of creation of pulmonary stenosis as a palliative procedure for patients with ventricular septal defects. There were 13 patients so treated (8 survivors). Quite correctly, they do not recommend this procedure in lieu of definitive closure. One of the occasional serious complications of closure of septal defects has been the occurrence of complete heart block. The use of isopropyl-*l*-arterenol (Isuprel; isopropyl-*l*-norepinephrine) has been found effective in management of this complication (65).

Pulmonary hypertension.—Early in the experience with ventricular septal defect closure it became evident that the type and degree of the pulmonary vascular pathologic changes were the most important determinants of the operative risk. Patients with pulmonary hypertension and no appreciable systemic arterial desaturation, but with widespread and severe pulmonary arteriolar occlusive disease due to intimal proliferation, rarely have survived closure, however expeditiously the operative procedure may have been carried out. Whereas other patients, with equal or perhaps even higher pulmonary arterial pressures and also with no detectable difference in their systemic arterial oxygen saturation, have survived closure with curative results and are known (from lung biopsy) to have had only medial hypertrophy with perhaps some scattered intimal proliferation. In predicting the risk for a given patient with severe pulmonary hypertension the usual physiologic data obtained from heart catheterization have proved to be of surprisingly little value in deciding the feasibility of corrective surgery in specific instances (66). Dushane *et al.* (67, 68) report similar findings in respect to the usual physiologic data obtained at heart catheterization and have suggested that the electrocardiogram was of most value to them in assessing operability. That is, in a particular patient with severe pulmonary hypertension, they would recommend closure of the ventricular defect only

if there was a pattern of left ventricular diastolic overloading.

In assessing their own experience with this problem, the reviewers have found that the use of the diastolic overloading pattern to determine operability would have eliminated many of the patients with occlusive intimal arteriolar disease who did not survive closure procedures. However, unfortunately, its use would also have eliminated almost twice as many patients with equally severe lesions physiologically but in whom closure was successful with a curative result. These latter patients were found, upon study of their lung biopsies, to have pulmonary vasculature which was usually abnormal but the changes were confined to medial hypertrophy and only scattered or moderate intimal proliferation. Because Adams *et al.* (66) have found that differences in the lung biopsy have been the only accurate and consistent differential finding known to date between these two groups of patients, the University of Minnesota group has turned to its use in deciding operability in these questionable patients.

Dammann *et al.* (69, 70) and Ferguson *et al.* (71) have reported the experimental production of pulmonary vascular disease. They confirm previous experiments, which show that an anastomosis between the aorta and pulmonary artery will cause a gradual medial hypertrophy of the more muscular branches of the pulmonary artery followed by spotty intimal proliferation. A much more dramatic effect is obtained by end-to-end anastomosis between a systemic artery and a lobar pulmonary arterial branch; this results in an acute arteritis of the smaller muscular vessels. Healing occurs gradually after removal of the shunt by the replacement of the affected vessel with a fibrous mass embracing a few recanalized areas and by a proliferative group of endothelial cells and blood spaces. Vagotomy and sympathectomy do not affect the result.

Summary and conclusion.—In view of the fact that corrective surgery for ventricular septal defects is now a feasible procedure and since it is a well documented fact that, rather uniformly, patients with these defects are seriously ill and have a severely shortened life expectancy, it would seem currently worthwhile to balance for each patient the increasing hazard of procrastination against the decreasing operative risk.

Tetralogy of Fallot

The availability of a curative as well as a palliative procedure for these individuals has created a dichotomy in their management at present. On the one hand the University of Minnesota group (72, 73) has advocated and has performed the curative procedure (closure of the ventricular septal defect and relief of the pulmonic stenosis) on all patients with tetralogy in need of operative help since 1954. On the other hand some still prefer the shunt operation (74, 75).

Potts *et al.* (76) have followed up their first 100 cases for six to eight years. There were 99 aorto-pulmonary anastomoses and one subclavio-

pulmonary shunt. The followup was 100 per cent. The immediate mortality was 9 per cent, mainly in children under the age of three years, and there were five late deaths; four cases required a second operation. Of the 86 survivors, 68 led virtually normal loves, 16 had a fair result, and one a poor result; one was unimproved by operation. Cardiac enlargement occurred in 51 cases, in the majority soon after operation.

McCord & Blount (77) describe one case of aneurysm of the infundibulum developing eight weeks after infundibular resection, and another who developed functional pulmonary insufficiency with a large left to right shunt one year after operation. They concluded, as Brock has long emphasized, that the "overriding" aorta does not compensate for the systolic pressure differences between the right and left ventricles following infundibular resection. Officer Brown (78) has collected the results in 240 patients treated by palliative operations. Two hundred and four shunts were performed with an overall mortality rate of 12 per cent. There were 30 direct operations only, and is this group the mortality was 33 per cent. In the shunted cases, the Potts operation gave slightly better results than the Blalock operation, but the mortality rate was slightly higher.

White *et al.* (79) have found that 163 or 32 per cent of 500 patients followed five to eight years after a Blalock-Taussig operation for pulmonary stenosis or atresia were known still to have a good result from their shunt. Not all of these patients had the tetralogy complex, and among the 212 tetralogy patients who survived their initial operative procedure, and in addition were improved by it, 69 per cent were still in the good result group five to eight years later, whereas the other 31 per cent had died or had developed complications which had downgraded their classification. These results are good, but illustrate the well-recognized fact that inevitably the mortality associated with palliative surgical procedures will continue to rise at an abnormal rate with the passage of time, whereas with any curative procedure, it is pertinent to point out that virtually the entire morbidity and mortality are the initial ones.

Summary and conclusions.—The shunt operations of Blalock, Taussig, and Potts have brought effective palliation into the lives of many previously crippled from the physiologic abnormalities associated with Fallot's tetralogy. The late failures recorded are most often not related to the closure of a previously functioning shunt, but rather to the patient "outgrowing" his shunt. This same fact explains why the results of the shunt operation have been generally poor both in infants and in adults.

The only logical goal in any individual patient, and hence the one we all seek, is the complete correction of all existing cardiac defects by open cardiotomy using a pump oxygenator. After having thus restored the circulation to normal, anatomically and physiologically, one can for the first time hope that life expectancy thereby can be lengthened to its full span. The full acceptance by all of this obvious goal is merely a matter of time.

Pulmonary Valve

It is now well recognized that isolated pulmonary valvular stenosis is not such a rare lesion as it once was thought to be. Experimentally it has been produced in dogs under hypothermia and inflow stasis by Riberi *et al.* (80). Defects in the atrial septum were produced either before or after the valve stenosis. In all dogs a significant rise in right ventricular pressure was obtained with a pressure gradient across the sutured valve. In addition, a right to left shunt occurred in two dogs at rest and in the remainder on exercise.

The effect of pulmonary valvectomy was studied by Fowler *et al.* (81). Under normal conditions, no rise in the end-diastolic right ventricular pressure was found; presumably, the regurgitation was insignificant at the low pressures obtaining in the pulmonary circuit. But if acute pulmonary hypertension was produced by clamping one pulmonary artery and partially occluding the other, more striking changes in the end-diastolic pressures resulted. However, no dog showed any signs of right ventricular failure for the ensuing six months.

Lillehei *et al.* (82) produced a significant fall in right ventricular pressure after Brock valvotomy in 15 cases out of 20 who were studied some months after operation by recatheterization. They conclude that the five failures were a result of either undetected associated infundibular stenosis, unrecognized septal defects, or, in a few of the early cases, to a failure to dilate vigorously the valve orifice after passing the valvulotome. Even in the successful cases, however, the right ventricular pressure was still twice as high as normal and they suggested that a more extensive procedure under direct vision is indicated.

Silverman *et al.* (83) record three deaths on the table, all in cases operated on while in right ventricular failure. They divide their cases into three groups: group I has a very high right ventricular pressure and may die in infancy; group II has a right ventricular pressure over 100 mm. Hg, is symptomatic, and requires operation; If group II cases, are symptom free, they are observed closely every three to six months; group III has a pressure below 100 mm. Hg and only mild ECG changes. They do not advise operation in these cases as from their observations, operation (done by closed technique) is unlikely to lower the right ventricular pressure.

Hosier *et al.* (84) followed 69 cases after the Brock operation. The operative mortality was 8 per cent, and there was subjective improvement in all survivors except two. The oxygen saturation and hemograms improved in all except one, and this patient was thought to have some anomaly of the pulmonary venous return. Though a diastolic murmur occurred in 15 cases after operation, in none of them was the liver engorged. It was found that in those patients in whom the right ventricular pressure was reduced below 100 mm. Hg, the size of the heart returned to normal. On this basis, the authors concluded that these patients had obtained an excellent result from surgery. This reviewer would disagree rather completely with the latter

viewpoint, since pulmonary valvular stenosis is a defect that can be a completely curable lesion; we believe, therefore, that palliation should not be acceptable. Children, especially, with residual pressures of 50 to 100 mm. Hg in their right ventricles, are almost certainly headed for future trouble.

By use of a direct visual approach and hypothermia, Swan & Blount (12) have reported excellent physiologic results in relief of pulmonary valvular stenosis. The reviewers also favor the direct vision approach for this lesion, but prefer the pump oxygenator at normal body temperature, since it allows a greater latitude in managing the unanticipated associated defects which may require ventriculotomy or atriotomy. Kay *et al.* (35) have expressed a similar viewpoint.

Patent Ductus Arteriosus

Waterman *et al.* (85) reviewed 3896 cases collected from various centers. Two thousand nine hundred twenty-nine were under 14 years of age. Sixty nine per cent of these were symptom-free, whereas only 48.5 per cent of those over 14 years of age were symptom-free. Twenty-seven and four-tenths per cent of the children had symptoms of myocardial insufficiency, whereas 40.8 per cent of adults fell into this category. Finally, only 3.7 per cent of ducts in children were infected but 10.7 per cent of adult ducts were in that condition. The overall operative mortality for correction was 2.77 per cent; in children it was 2.3 per cent, whereas in adults it was 5.5 per cent, i.e., more than twice as high. Satisfactory postoperative results were obtained in 98.3 per cent of children and in 95.5 per cent of adults. Sixty per cent of surgeons favored division, 33 per cent ligation, and the remainder varied their technique from case to case. Strikingly enough, the overall mortality was the same for both procedures, but in adults the mortality for ligation was 4.3 per cent and for division 5.2 per cent. It is now agreed that in reversed ductus shunts the duct should not be interrupted unless it can be shown that the pulmonary artery pressure drops on temporarily occluding the duct. Seven and one-tenth per cent of the cases had aneurysms associated with the patent ductus, pulmonary artery, or aorta. Analysis of deaths showed that 29 resulted from hemorrhage, and six from cardiac arrest. The remaining nine were ascribed to various other miscellaneous causes. There were only five late deaths. The authors conclude that all simple patent ducts should be interrupted. The optimum age probably is between two and twelve years.

Bosher (86) has described a simplified step-by-step division-and-suture technique, and Glenn *et al.* (87) report a series of 110 consecutive ducts closed without mortality and with only one case of recurrent nerve palsy. They point out that most operations were carried out between the ages of three and nine years and that hemorrhage occurred frequently above the age of 30 years. They employed induced hypotension at the time the clamps

were placed on the duct in patients with serious pulmonary hypertension.

Gerbode & Holman (88) report that out of 170 cases, 20 required operation before the age of three years. Among these were two cases, only a few weeks old, in whom there was an associated coarctation. In addition, 11 patients had pulmonary hypertension, and in all seven cases were associated with coarctation. There were two deaths, one from hemorrhage and one from cardiac failure, the latter being one of the infants with coarctation. In the remaining infants under three years there was a systolic murmur only and an ECG of adult type, indicating left ventricular hypertrophy at this age. In the eleven children and adults with pulmonary hypertension there was a systolic murmur only, but the ECG showed right ventricular hypertrophy and the pulmonary artery pressure averaged 117/40 mm. Hg. The group in which there was an associated coarctation showed more severe symptoms than would be expected from the coarctation alone. They conclude that a large pulse pressure differentiates those cases with systolic murmurs only from cases of ventricular septal defects, but this may not be reliable if there is pulmonary hypertension.

Davis *et al.* (89) list a number of conditions which may simulate patent ductus, and describe a case of aortic-pulmonary window closed by ligation, one case of patent ductus probably associated with a ventricular septal defect, an anomalous left coronary artery emptying into the right ventricle which was excised and and ligated, and an aneurysm of the sinus of Valsalva communicating with the right atrium. They suggest that, in cases of doubt, cardiac catheterization and retrograde aortography be used to differentiate these conditions from patent ductus. Vaysse *et al.* (90) record a case of an aortic-pulmonary window which was closed under hypothermia by suturing the defect through the open pulmonary artery. The systolic murmur persisting postoperatively was attributed by them to deformity of the aortic valve and aorta, possibly caused by sutures.

Summary and conclusion.—The most important fact about patent ductus arteriosus is that its mere presence, except in infants who are asymptomatic, is an indication for surgical treatment unless unusual and compelling contra-indications exist.

Coarctation

A series of 93 cases treated by ten surgeons is reported by Hayward (91). Of these cases, three were inoperable. Eight-one direct anastomoses were performed, seven grafts were inserted, and two subclavian-aortic anastomoses were done. The operative mortality for the whole group was 9 per cent. There were no aneurysms but there were seven associated patent ductuses, two of them distal to the coarctation. In addition, other associated abnormalities included one persistent left superior vena cava, one retro-esophageal right subclavian artery, four ventricular septal defects, and one atrial septal defect. Eight cases had aortic incompetence and three had

aortic stenosis. The postoperative fall in blood pressure was unrelated to symptoms and the blood pressure sometimes took longer than two months to reach its final level.

The blood pressure changes following resection of coarctation have been carefully studied by Counihan (92) in 20 cases operated upon by one surgeon at one hospital. Statistically significant decreases in both systolic and diastolic pressures occurred after resection, but the end pressures were still higher than in the normal population. That this was not because of incomplete restoration of lumen is shown by the fact that (*a*), collateral vessels disappeared after operation; (*b*), the delay in the femoral pulses was abolished; and (*c*), the femoral systolic and diastolic pressures were equal to the brachial ones. The femoral diastolic hypertension found before operation persisted. He concludes that the restoration of a full aortic lumen is only one factor in the reduction of the blood pressure. In addition, there was a generalized increase in peripheral resistance, probably caused by developmental narrowness of the small arteries. The patients in this series were observed from three to 51 months.

Sellors (93) gives the incidence of aneurysm associated with coarctation as 7 to 8 per cent. They occur usually where a branch is given off, and may be associated with cerebral berry aneurysms. At the site of aneurysm formation, the intima and the muscular part of the media are intact but the concentric elastic fibers are interrupted by the muscle fibres of the smaller, and therefore more muscular, branch. Mycotic aneurysms also occur distally in the area of "slack water." He inserted aortic grafts in his three cases and these have functioned without symptoms for three to four years.

Minor *et al.* (94) record coarctations treated in infants at the age of two weeks and 30 weeks. These patients may present as acute emergencies with unexplained heart failure in infancy; angiocardiography for diagnosis may be necessary. Coarctation in infants with heart failure is attended by a considerable mortality if left uncorrected. Thus Ober (55) at the Boston Lying-In Hospital found eleven patients with coarctation among 100 infants dying within one month of birth. Similarly, d'Abreu & Parsons (95) found that between 1950 and 1955, 30 infants died of coarctation of the aorta within six months of birth (all without surgical treatment) in their Children's Hospital. They have reviewed their results of surgical treatment and have concluded that if a baby has coarctation of the aorta and symptoms of heart failure, and if the failure is slow to respond to medical management, death is probable within the course of a few months unless treated surgically.

Mitral Valve

The largest number of cases recorded in the literature of mitral valvotomy adequately followed is that of Harken (96) and Harken & Black (97). The mortality in this series was 14 per cent for group II and III cases in

the first 100, but dropped to 0.5 per cent in the last 200. In group IV cases the corresponding mortality was 16 per cent of 251 cases. It is pointed out that all group IV cases were in group III at one stage of their disease, when the operative mortality was 40 times lower. Also, the postoperative rehabilitation is much better in groups II and III than in group IV. Thus, in the first 500 cases 75 per cent of group II and III cases were improved, but only 55 per cent of group IV; and in the last 500 cases these figures rose to 90 per cent and 65 per cent respectively, the improvement being mainly owing to the fall in mortality. The chief source of morbidity and mortality was found to be embolism. These authors therefore believe that carotid occlusion is necessary during the intracardiac manipulations. There were 12 reoperations, but these were all necessitated, in their opinion, by inadequate initial operations in which only the valve ring had been stretched. Concomitant aortic stenosis was corrected by finger fracture through an operating tunnel sewn onto the aorta. Tricuspid stenosis, when it was found, was also treated by finger fracture.

Glover (98) has analyzed 50 patients operated upon five to six and one-half years ago. There were three deaths in the first few postoperative months, two from mitral incompetence and one from shock. Six deaths occurred in the first three years. These cases all had extensive disease with severe valvular calcification and immobile valve cusps. Forty-one patients were alive, and of these 30 were improved on the assessment of the surgeon and the cardiologist alone, but this figure rose to 36 if the views of the family physician and patient were taken into account. The heart size had decreased or had remained stationary since operation in 87 per cent. In general, the improvement obtained in the first year following operation was maintained. Bailey *et al.* (99) emphasized that the right thoracotomy incision offers technical advantages over the conventional left incision for performance of mitral commissurotomy. Milnor (100) has reported similar figures for the first 150 cases operated upon by Blalock. The most important factor influencing the result was the presence of mitral incompetence and its degree. The incidence of embolism was four times as high in the patients with atrial fibrillation, but the results, apart from the effects of embolism, were not affected by the presence of atrial fibrillation *per se*. Of interest is the fact that, in this series, the post-commissurotomy syndrome was said to occur up to four years after operation, and that five patients with prolonged symptoms and signs of this syndrome developed cardiac failure from which two of them died.

Windsor (101) has reported a series of 643 cases with 75 per cent good and moderately good results; this is in accord with other reports. Baker *et al.* (102), in their three year follow-up, point out that the size of the heart, degree of disability, and the presence of atrial fibrillation did not influence the results of operation, but that the results are better in those patients in whom the valve orifice was found to be 1 cm. or less in diameter at opera-

tion. This may be a critical size for the valve orifice, patients with smaller orifices seeking advice sooner and therefore sustaining less myocardial and cusp damage. Pulmonary hypertension is an operative indication and a good relief of the stenosis will lower the pulmonary artery pressure. Three patients who developed irreversible atrial fibrillation after operation all did poorly.

Baronofsky *et al.* (103) described five reoperations. In one of these cases predominant mitral incompetence had been found at the first operation, but extensive calcification had produced predominant stenosis during the interval between operations. In all cases the stump of the appendage was used. Bailey's approach through a right thoracotomy may facilitate reoperation.

Mitral valvotomy may be necessary in the younger age group, as pointed out by Angelino *et al.* (104), who found eleven patients between the ages of eight and sixteen years in 600 valvotomies. The orifice was less than 1.2 cm. across in all but one. There was no evidence that reactivation of rheumatic fever was more frequent in this group than in the older age groups; nevertheless they advise prolonged therapy with penicillin, ACTH and salicylates.

Bruce *et al.* (105) conclude from their pre- and postoperative study that the standard exercise test on the treadmill gives the best indication of improvement likely to be obtained from operation. Papp & Zion (106) give an account of the post-commissurotomy syndrome. They concluded that the bloodstained effusion they found so often was due to oozing from the appendicular stump.

Mitral Regurgitation

Benichoux & Chalnot (107) describe an experimental method for the correction of mitral incompetence by placing a plexiglass sphere under the posterolateral cusp. The sphere is fixed in this position by a transventricular screw and lock nut. DeWall *et al.* (108) have described experimental results with the use of an Ivalon prosthesis inserted by digital guidance and anchored through the area of incompetence, but Glenn (109) has reported disappointing results with the use of this method. Davila *et al.* (110) have advocated insertion of a circumferential suture about the annulus of the the mitral valve, and have reported their use of this method in seven patients with three deaths. Bailey (111) has described a method of crossplication of the incompetent pole of the mitral valve by inserting the necessary sutures by digital guidance. The reviewers (112) have reported a small series of patients either with mitral regurgitation or mitral stenosis (complicated by additional factors) treated under direct vision utilizing the pump-oxygenator. The surgical exposure of the mitral valve for the open operation has been most successful through a right thoracotomy and a left atriotomy.

Summary and conclusions.—The most notable reports in regard to the surgical treatment of mitral stenosis during the past year have emphasized the steadily declining operative risk, as well as the long term follow-up

results which have verified that, by and large, these benefits are likely to be lasting for most patients.

The surgical attack on mitral regurgitation by closed and now by open methods continues. Valvoplasty by the open approach has appeared to offer these patients with mitral regurgitation substantial benefits.

Aortic Valve

Bailey *et al.* (113) discuss the results of the transaortic approach to the aortic valve. A cuff of pericardium was sutured to the aorta, and through this the exact extent of the disease was assessed with the finger. Finger fracture or valvotomy, using a sickle-shaped knife, is then performed. They consider that the valve area has to be reduced to 10 per cent of normal before significant symptoms arise. A total of 287 valvotomies have been performed using either the transventricular or transaortic route. Some of these had associated mitral stenosis. The mortality rates for the two routes were 45 per cent and 31 per cent respectively for isolated aortic stenosis, and 23 per cent and 7.1 per cent (in only 14 cases) for combined aortic and mitral stenosis. The authors favor a right-sided approach, which they describe, as it allows them to do a triple valvotomy, should this be necessary.

The same group (114, 115) analyzed 40 cases of transaortic valvotomy and demonstrated a considerable drop in mortality, but found no change in the incidence of postoperative valvular incompetence. Furthermore, postoperative improvement was closely related to valve mobility. Mobility and degree of calcification were also related, but there was still a proportion of cases with severe calcification and yet some valve mobility. At present, there is no way of differentiating between these. The operative failure rate therefore, will still be high. They advocate early operation before severe valvular damage and calcification occur.

Baker & Campbell (116) point out that aortic stenosis has a prognosis of less than two years after the onset of severe symptoms, in marked contrast to mitral stenosis where the prognosis is in the region of five to ten years. The main obstacle to achieving a good operative result is calcification, which makes it difficult to obtain an adequate valve opening without producing significant aortic incompetence. Moreover, the left ventricular approach means that operation must be undertaken before irreversible myocardial damage has occurred. The pattern of left ventricular strain in the ECG is the most helpful early index. As pointed out by Lillehei (45), the open transaortic approach allows better restoration of valve mobility; this alone is a powerful argument for employing cardiac bypass in these cases by means of a pump-oxygenator with retroperfusion of the coronary sinus (117) or induced asystole. He considers this method superior to the blind procedures, as it allows one to perform an accurate valvotomy, and the calcified excrescences on the cusps can be trimmed off with scissors without any danger of calcium embolism. Moreover, cusp mobility can be better restored by finding and

dividing the adhesions between the cusps and the adjacent aortic wall in the sinuses of Valsalva. Swan & Blount (12) and Lewis *et al.* (118) have each described three patients with aortic stenosis operated upon under direct vision, utilizing general hypothermia and inflow stasis. The insertion of a Hufnagel valve in cases of aortic incompetence improves glomerular filtration in the kidneys (119).

Summary and conclusions.—The experience with the closed operations for aortic stenosis has been substantial and the results for some patients spectacularly successful, but most surgeons cannot hide a certain disappointment with the overall results. The accurate separation of all three cusps under direct vision should prove to be a better operation, although it too may fail in certain of the valves destroyed by calcification. Aortic regurgitation remains a vexing therapeutic problem for surgeons to solve.

Coronary Arteries

Coronary artery disease is now the most important single cause of death in America. Interest in methods of treatment and prevention therefore is acute. Levy *et al.* (120) have produced good coronary angiograms in dogs using a catheter passed down to within one cm. of the aortic valves. The injection syringe was coupled electrically to the x-ray screen, and a single exposure produced good visualization of the coronary arteries. In 100 dogs there were no fatalities even with repeated injections, not even when a branch of the left coronary was obstructed by a Goldblatt clamp. A similar technique has been employed by Cannon *et al.* (121), but they used a double lumen catheter with a balloon at the end to block the aorta momentarily at the time of the radio-opaque dye injection. They also used four to ten times greater volumes relatively than those injected in human cases. Their mortality was no greater than that for the average air encephalogram. Excellent coronary visualization was obtained in this way, and they point out that the anterior descending branch can always be seen. Clearly, a reliable method of coronary angiography which is safe will have to be developed if a rational direct surgical attack on this form of arterial obstruction is to be devised.

Leighninger & Beck (122) studied the effect of sympathectomy and vagectomy on the intercoronary communications of the dog. They conclude, using the Mautz-Gregg backflow index as the measurement, that there is no vasomotor influence on the intercoronary vessels. Siderys *et al.* (123) ligated the great cardiac vein one month before ligating the anterior descending branch of the left coronary. Though this resulted in reducing the mortality by half or more, depending on whether the septal branch was included in the ligature or not, they found that simply opening and closing the pericardium gave equally good protection. Both procedures promote intercoronary flow and communications, and the major protection afforded by various procedures is due to this rather than to the supply of fresh blood brought to the

myocardium from without. The same group (124) studied the effect of ligating the anterior descending branch upon exercise tolerance of dogs. These animals had previously been trained to run on a treadmill to the point of exhaustion. Of 30 dogs, 16 died in the first 24 hours following ligation and two more in the next nine days. The remaining 16 showed no change in their exercise tolerances, though all of them had large infarcts at autopsy.

Carey *et al.* (125) have shown that collateral channels will develop in the normal nonischemic myocardium from a Vineberg internal mammary implant if a temporary fistula between this artery and the left atrium is created. Furthermore, when the subclavian artery was implanted instead, but without a temporary fistula, the infarcts resulting from ligation of the anterior descending artery were smaller. The larger subclavian artery is less liable to occlusion by intimal proliferation (126).

Experimental coronary embolism and occlusion have been produced by Munro *et al.* (127) by injecting plastic microspheres. These resulted in characteristic ECG changes and exercise intolerance. Interestingly enough, fresh infarcts developed following exercise months after the original injection.

Feil *et al.* (128) record their results in 61 cases treated by the Beck operations. Eight Beck I operations were performed without mortality and 53 Beck II operations with a 25 per cent mortality. The Beck II operation is a long and difficult procedure. Heart failure may develop, necessitating complete ligation of the coronary sinus. They conclude that the Beck I operation is suitable for cases invalided by pain which is not relieved by medical measures. Beck & Weckesser (129) record a case of ventricular fibrillation resulting from coronary infarction which was successfully resuscitated. The patient was leaving the hopsital after an ECG examination at the time of the attack.

Peripheral Arteries

The dynamics of flow in different sized tubes and in branched tubes have been simply and beautifully investigated by Wesolowski & Sauvage (130). Flow patterns of visible precipitates were photographed in glass models. It is an hydrodynamic principle that incompressible fluids will exhibit turbulence when passing to an expanded region. The higher the speed of flow, the closer to the origin of the expansion turbulence occurs. The forward kinetic energy is converted into static energy to a certain degree. From this it follows that, as a general principle, the best graft is an isodiametric one. The next best is one smaller in diameter than the host vessel, as the host vessel can withstand turbulence better than the graft. The worst variety from the hemodynamic point of view is a graft bigger than the host vessel. These studies also help to explain the development of poststenotic aneurysms and the tendency to thrombosis in oversized grafts.

Flow studies in branched models showed that very little, if any, tur-

bulence occurs at the sites of bifurcation such as the aortic bifurcation; but considerable turbulence occurs just distal to the origin of right-angled vessels such as the renal arteries and the celiac axis. This fits in well with the sites of occurrence of aneurysms of the aorta. The authors consider that this observation may help to elucidate the production of atherosclerosis, the eddy currents causing trauma, and the localization of small intravascular thrombi.

Determinations of flow in arteries exposed at operation have been made by Flores *et al.* (131) using a square wave electromagnetic flow meter. With their apparatus, the thickness of the vessel wall does not influence the reading. Clinical measurement of vascular insufficiency in the lower limbs has been done by Halligan *et al.* (132). They used radioactive iodinated serum albumin. With this method they have shown that vasodilator drugs have a measurable effect even after sympathectomy.

The fate of synthetic fibres when used as vessel grafts has been extensively investigated. Wesolowski & Sauvage (133) used large and fine mesh orlon tubes. A hematoma around the tube caused delay in the appearance of the intimal lining. Intima grows in from both ends of the graft and also through the interstices of the mesh from the fibrous tissue surrounding the graft. Edwards & Tapp (134) have used chemically treated nylon grafts. These were dipped in a solution of formalin, then crimped by threading them onto glass rods and heated to make them set. Porosity was thereby reduced and crimping allowed the graft to be bent to 180° without kinking. The ends were heat-sealed and the inside of the graft siliconed. Deterling & Bhonslay (135) used a similar calendering process to reduce the porosity of taffeta-woven fabrics of nylon and of dacron and obtained good results with these. Polyvinyl alcohol sponges (Ivalon) moulded into seamless tubes resembling the aorta and its branches have also been used successfully (136). Fifteen patients have had these Ivalon grafts implanted without sequelae. Lary *et al.* (137) have used tubes made from steel mesh cloth. These provoke no foreign body reaction whatsoever but the incidence of thrombosis is fairly high.

The composition of vessel grafts kept for long periods of time in nutrient media has been studied by Lazzarini *et al.* (138). By 40 days all cellular structure disappeared. Collagen fibres were still present up to 190 days, and the elastic fibres persisted longest, separating slowly after 500 days but still being present up to two years. Contamination or changes in pH caused the elastic fibres to fragment rapidly. Radio-sulfate was used by Bellman & Gothman (139) to show that homografts soon die when implanted. They concluded that the simplest storage method was the best, as the result does not depend on the viability of the graft. The fate of 1000 experimental homografts has been followed histologically by Sauvage (140). The junction between the graft and the host vessel healed by ingrowth of fibroblasts for one to two cm. in the graft and two to three cm. in the host vessel. The inner portion of the

graft fibre framework condenses to an acellular structure impervious to fibroblasts for one year. In this respect, this acellular structure is comparable to plastic tubes, but has the advantage of having elastic fibres in it. Most grafts longer than three to four cm. are devoid of an inner lining in their middle portions. An important observation is that in arteriosclerotic patients the graft is less liable to complications than the rest of the patient's arterial tree. Kanar *et al.* (141) have shown that homografts do not keep pace with growth of the host. Rosenberg *et al.* (142) used heterologous bovine grafts which had been enzymatically treated. These grafts are virtually reduced to collagen tubes. Experiments using these tubes have been 70 per cent successful up to one year. Grafts and patches made from skin and from fascia are unsafe and should not be used (143, 144).

The result of thromboendarterectomy in 97 cases was described by Wylie (145). In the aorta 92 per cent good results were obtained, and in general, the higher the lesion and the more localized the changes, the more satisfactory were the results of this type of operation. Mavor (146) analyzed 149 cases of atheroma of the lower limbs accompanied by secondary thrombosis. Arteriography and exploration were carried out in every case. Main vessels, i.e., those above the knee, were affected nine times more often than those below the knee, but the profunda femoris was rarely involved. The extent of the collateral circulation determined the extent of the secondary thrombosis. In the femoral artery, thrombosis usually was propagated proximally as far as the profunda, but in the popliteal artery the spread of thrombosis progressed distally. Early treatment therefore is necessary to prevent the spread, and end-to-side bypass of the affected arterial segment is considered to be the operation of choice as it leaves the collaterals undisturbed.

The role of sympathectomy in the treatment of vascular insufficiency of the lower limbs has been investigated by Edwards & Crane (147) and by Hoffert (148), and this line of treatment offered best results in patients under the age of 55 years. They consider that it should be regarded as a definitive approach rather than as a last resort in the hopeless case.

Crawford *et al.* (149) conclude that bypass of long-obstructed segments offered a better prognosis than excision and end-to-end suture, provided that there is adequate outflow in the distal vascular bed beyond the obstruction. This view is also shared by Hufnagel (150) who reported 90 per cent good results in obstruction situated entirely above the inguinal ligament. Below this level, 70 per cent satisfactory results were achieved if a good pulsatile flow was established. However, Hoye & Warren (151) in their series of iliofemoral reconstructions by homografts, saphenous vein, and superficial femoral vein autografts showed that 70 per cent had become occluded up to two and one-half years after operation. Horton (152) achieved somewhat better results, only seven out of 29 homografts becoming occluded in 17 months. Warren (153) has used a homograft between the splenic and

iliac or femoral arteries to bypass obstructions in predominantly unilateral cases where, for some reason, a direct attack on the segment was contra-indicated. The splenic artery carried enough blood to relieve pain in the limb and the use of a graft obviated extensive dissection of the splenic artery. Reversed saphenous vein autografts have been used to bypass femoral artery obstructions by Murphy & Aust (154) with success, except in two cases where an attempt was made to bypass an aneurysm. The long-term results of vein grafts are reviewed by Dye *et al.* (155), who showed that 50 per cent failed early, but that the remainder functioned well up to four years with the development of only localized aneurysmal pockets and no generalized widening.

Rob, Eastcott & Owen (156) reviewed the history of the surgical treatment of diseases of the aorta and peripheral arteries and concluded that, ultimately, artificial prostheses will be perfected. Thromboendarterectomy yielded poor results in their hands. Leaking aneurysms are emergencies, but with adequate supplies of blood, such patients can be saved by emergency surgery. They have performed 194 arterial reconstructions of all sorts.

Aortic Aneurysms

Brindley & Stembridge (157) have studied 369 cases at necropsy. The over-all incidence was 4 per cent. Aneurysms of the arch occurred at lower age groups and specific infection was the etiologic agent in 50 per cent. Dissecting aneurysms are associated with cardiac hypertrophy in 80 per cent of cases. Rupture of the aneurysm was the commonest cause of death.

Cooley *et al.* (158) described their technique of excision of an aneurysm of the arch using a temporary Ivalon bypass together with surface cooling. The patient died six days after operation without regaining consciousness, but the Ivalon graft was found to be working well. DeBakey (159) suggests that dissecting aneurysms can be treated by re-entry of the dissecting part into the aortic lumen and closing the two layers of the double lumen below the point of re-entry. This allows peri-aortic fibrosis to strengthen the wall of the outer lumen. A second alternative is the excision and grafting of the vessel at the point of dissection, with obliteration of the lumen below the lower suture line. DeBakey *et al.* (160) described four patients with extensive aneurysms of the thoraco-abdominal aorta involving the celiac, superior mesenteric, and renal arteries; there were two survivors after excision of the aneurysm and homograft replacement. Deterling & Bhonslay (135) have treated 70 aneurysms of the aorta by excision and graft, using a woven graft with good results. Ada & West (161) excised two saccular aneurysms of the arch, closing the necks in each case by lateral suture, and homografted three fusiform aneurysms of the abdominal aorta.

Veins

Sauvage & Wesolowski (162) have shown that in the growing pig fresh venous autografts maintain the characteristics of normal vein. There is

normal anastomotic growth, provided that there is no suture restriction. In fact, there is a close similarity between the venous and arterial systems of the growing pig with regard to the fate of fresh autografts. Aortic and orlon cloth grafts were unsuitable in the venous system.

Blum *et al.* (163) described a very interesting and unusual case of agenesis of the postrenal portion of the inferior vena cava treated with success by the insertion of an aortic bifurcation homograft. Ashburn *et al.* (164) used aortic homografts to replace the superior vena cava in dogs, but found stricture formation at the site of aorto-atrial anastomosis. In one patient this operation was performed for malignant superior vena caval obstruction, but a short cuff of the vein was preserved inferiorly. The patient was alive and well seven months after receiving in addition a course of radiotherapy. The primary tumor was not surgically removable in this patient.

Murphy *et al.* (165) described the obliteration of varicose veins by the insertion of an intraluminal suture. Moore (166), on the basis of venography in post-phlebitic legs, advocates the ligation of incompetent superficial femoral, saphenous and deep communicating veins. His treatment in these distressing cases consists of this ligation, a Kondoleon operation of the Homan's type, and excision with skin grafting of all ulcers. These procedures are performed at one session. Sixty cases treated by him have yielded results considered better than those managed by prolonged nonoperative care.

Miscellaneous

A ventricular aneurysm treated by the application of a free muscle graft taken from the pectoralis major is described by DeGoudart d'Allaines *et al.* (167). In Germany three similar cases have been treated by using a free full-thickness skin graft. Bailey has described the successful resection of a ventricular aneurysm (111).

Nichols (168) has developed a fishnet type of instrument for the removal of benign pedunculated tumors of the left atrium. He operated on five patients; of these four died without the use of the net, but the last one survived when the net was used.

Baffes (169) has partially corrected a transposition of the great vessels by interchanging the right pulmonary veins and inferior vena cava using an aortic homograft. However, partial correction in multiple stages by a similar technique yielded only seven long term survivors out of 32 patients treated (170). The obvious solution to this common and vexing problem is a complete correction at one stage utilizing the pump-oxygenator.

Niden *et al.* (171) have reproduced pulmonary embolism using beads injected into the right ventricle. There was an immediate bradycardia and apnea of vagal origin followed by sympathetic respiratory stimulation. Also, there was a fall in oxygen saturation of the peripheral arterial blood; this was corrected or prevented by giving 100 per cent oxygen. The pulmonary hypertension which developed was partly due to mechanical obstruction, and partly to vasospasm locally, spreading to include the whole vascular bed of

the lung. Pulmonary arteriovenous communications are opened up by embolization, thus seemingly exaggerating the anoxemia, but lowering the pulmonary artery pressure.

Damage resulting from inflow stasis can be diminished if the heart is resuscitated by massage and not allowed to overfill when the caval tapes are released (172). Heparin had no lessening effect upon the extent of cerebral damage due to hypoxia.

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MEDICAL DISEASES OF THE KIDNEY[1,2]

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This review is based on the literature concerning medical diseases of the kidney published during the period 1954 through July, 1956. References to renal biopsy and acute renal failure are omitted since these subjects were reviewed in last year's *Annual Review of Medicine*. Further, limitation of space permits reference to only a fraction of the papers published during the selected period on medical diseases of the kidney. For this reason the reviewer has been forced to omit a number of references to every disease discussed. Likewise, space does not permit systematic review of purely experimental work in renal disease.

Several books of interest to the student of renal diseases have been published recently. The fifth edition of Fishberg's "Hypertension and Nephritis" (1) appeared in 1954. Many sections have been rewritten and brought up to date, especially those relating to renal function. This book continues to reflect the author's thoughtfulness and wealth of clinical experience. Homer Smith has written an excellent and concise monograph on renal physiology (2), while Elkington & Danowski have published a book on fluid and electrolytes (3) which contains much useful information applicable to renal disorders. A symposium on diseases of the kidney (4), comprising 13 articles and mostly written in textbook style, appeared in 1955.

Among papers of general interest is that of Mellors & Ortega (5), who applied Coons' technique for detecting specific proteins in histologic sections to the study of kidney disease. They found that gamma globulin was localized in the glomeruli in lipoid nephrosis, glomerulonephritis and renal amyloidosis, and in the small renal arteries in periarteritis nodosa. They believed that their observations lent support to the hypothesis of an antigen-antibody etiology for these diseases. Marshall (6) studied the shallow scars seen on the surface of kidneys of patients of all ages. He found an incidence of 62 per cent in 448 autopsies, and believed that they were the result of maldevelopment rather than of vascular or infectious origin. Further, a correlation of these scars with hypertension was noted. Lange *et al.* (7, 8) found that complement was reduced in all of 40 patients with acute or subacute glomerulonephritis and in 27 of 29 patients with the nephrotic syndrome. The decrease was not caused by loss in the urine and was independent of changes in serum oncotic pressure. Further, fraction 4 was the limiting factor in acute

[1] The survey of literature pertaining to this review was completed in July, 1956.

[2] The following abbreviations are used in this review: GFR (glomerular filtration rate); RPF (renal plasma flow); C_{CR}, C_{IN}, C_{PAH} (clearance of creatinine, inulin, or para-amino-hippurate); Tm_{PAH} (tubular excretory capacity for para-amino-hippurate).

glomerulonephritis and fraction 2 in nephrosis. Although "telescoped urinary sediments" are typical of visceral angiitis or systemic lupus erythematosus, Schreiner (9) indicated that they were not specific and described such sediments in three patients with chronic glomerulonephritis. Baldwin and coauthors (10) applied their techniques for measuring the renal concentrating operation to 25 patients with renal disease. This involved measurement of osmolar clearance in hydropenic subjects during osmotic diuresis. By subtracting the urine flow from the osmolar clearance they calculated the volume of solute-free water reabsorbed by the tubules, which at high urine flows was constant, and then related this value to GFR. Their studies revealed a substantial concentrating ability in all patients with glomerulonephritis despite fixed specific gravities by the usual concentration test. In early glomerulonephritis GFR was impaired without alteration in the concentrating operation in contradistinction to late chronic glomerulonephritis when concentrating power was often decreased more than GFR. In recovery from acute renal failure their data suggested specific damage to the concentrating mechanism. In another new approach to evaluation of renal function Kaye (11) administered a single oral dose of a carbonic anhydrase inhibitor to 15 patients with renal disease. Although renal disease decreased the normal response (increase in urine flow and pH along with increased rates of Na^+, K^+ and bicarbonate excretions), metabolic acidosis alone (so often present in renal insufficiency) caused complete inhibition of the normal response. In a study of 41 children with chronic renal disease, West & Smith (12) found that acidosis, or low caloric intake, or both, accounted for all 21 instances of growth retardation present in the group. Von Glahn (13) described three instances of advanced renal insufficiency that exhibited necrosis of the islands of Langerhans at autopsy. Only one of these had traces of sugar in the urine. Happs & Wissler (14) described in 62 per cent of 107 uremic patients a pneumonitis characterized by slight to moderate edema, a fibrin network, a few red blood cells and macrophages which they believed sufficiently distinctive to warrant the designation "uremic pneumonitis." Pericarditis occurred in 60 per cent and colitis in 24 per cent of the same group. Wacker & Merrill (15) found that approximately half of their patients with uremia because of chronic renal failure had fibrinous pericarditis in contrast to only 18 per cent of patients with acute renal failure. The average duration of life in the chronic group was ten days after the detection of the pericarditis. Derow (16) has written an informative review of cardiac abnormalities in both acute and chronic renal diseases.

Proteinuria.—King, in two papers (17, 18), reported his observations on proteinuria in large numbers of young men in military service. In the first report on 3309 subjects he found 73.4 per cent had intermittent proteinuria (one-half of these were orthostatic), 16.4 per cent had continuous proteinuria (the majority due to overt chronic glomerulonephritis or presumably latent nephritis, and only a few the result of pyelonephritis), while the remainder had irregular or uninterpretable proteinuria. In the second paper on 15,000

subjects he found that the majority of instances of proteinuria were merely transient and of no significance. Five per cent were continuous in nature, while 15 per cent were orthostatic in origin. A brief follow-up study of some of the subjects with orthostatic proteinuria revealed that in 80 per cent the condition persisted. In contradistinction to Fishberg (1), King believed that some instances of orthostatic proteinuria were caused by organic disease. On the basis of indirect evidence obtained from the literature and his own studies, Löwgren (19) believed that benign proteinuria was attributable to post-tubular admixture of renal lymph fluid with urine. Lathem *et al.* (20), in a study of the effect of orthostasis on proteinuria in 19 patients with acute and chronic renal disease, found that urinary protein concentration frequently increased but that protein excretion rate decreased presumably because of the associated decrease in GFR. A number of electrophoretic studies of urinary proteins have been reported. In one such study, Sellers & Marmorston (21) found that the major fraction of urinary protein in renal disease, multiple myeloma excluded, was similar to plasma albumin. Generally, globulin excretion was also increased. Again with multiple myeloma excluded, variations among individuals suffering from the same renal disease were too great to permit diagnostic value. Heymann, Gilkey & Lewis (22), however, in a study of 11 cases of acute nephritis and 32 cases of nephrosis, found that less globulin was excreted by the patients with acute nephritis than by the patients with nephrosis although the albumin-globulin ratio was lower in the cases of nephritis, and that excessive globulinuria in the cases of nephrosis indicated a poor prognosis. Hardwick & Squire (23) studied the clearances of various protein fractions in patients with renal disease following infusions of human serum albumin. The clearance of globulins increased proportionately to that of albumin. They concluded that proteinuria potentially could result from increased glomerular permeability and decreased tubular reabsorption of protein. Chinard *et al.* (24), however, from calculations of albumin clearances and minimum concentrations of albumin in the glomerular filtrate in nephrotic subjects given albumin infusions, concluded that proteinuria was the result of increased permeability only. James *et al.* (25), using dextran infusions, came to the same conclusion. Lauson *et al.* (26) and Stickler *et al.* (27) presented data interpreted as evidence that corticotropin decreased the glomerular permeability in nephrotic patients. A discussion of proteinuria would not be complete without reference to a series of impressive papers by Oliver and co-workers (28 to 33) on cellular mechanisms of protein metabolism in the nephron. In experimental animals, using a variety of histochemical, enzymatic and immunologic techniques, they demonstrated that proteins which passed the glomerular filter were in part absorbed by the proximal convoluted tubule cells with no apparent alteration of the cytologic pattern. However, if the capacity of the tubules to absorb protein by the usual process was exceeded, an accessory mechanism of droplet formation became apparent. The mitochondrial rodlets took part in this process, apparently through enzymatic activity. Somewhat similar processes were con-

cerned with amino-acid reabsorption by the renal tubules. Allen (34) criticized Oliver's viewpoint but presented no substantial data.

Glomerulonephritis.—Clark (35) classified 265 children with glomerulonephritis according to Ellis' Type 1 and Type 2 criteria. Two hundred and thirty-nine conformed "fairly closely" to Ellis' Type 1 nephritis, while only eight were Type 2. The remainder fell somewhere between the two categories. The author stated that Type 1 and Type 2 nephritis were merely variations of a single disease. Kunstadter & Rosenblum (36) reported what they believed to be the first case of glomerulonephritis in a prematurely born infant who developed the nephrotic syndrome on the ninth day of life. Subacute glomerulonephritis was found at autopsy after death on the 72nd day. Claireaux & Pearson (37) reported chronic pyelonephritis in a newborn infant. The glomeruli, however, presented an unusual proliferative picture. Fison (38) described fatal acute glomerulonephritis in two successive infants in the same family, both at approximately six months of age. There was no known etiology. Some glomeruli showed crescents while hyaline thrombi blocked other glomerular capillary tufts.

Interest in the relation between hemolytic streptococcal infections and acute glomerulonephritis continues. Stetson *et al.* (39) reviewed their experience with an outbreak of acute glomerulonephritis in a military installation involving 180 patients with hematuria, 147 of whom had other signs of the disease. These cases were associated with an epidemic of hemolytic streptococcal infections. Of 184 patients whose throat cultures revealed Type 12 hemolytic streptococci 12 per cent developed nephritis, while none of 146 patients whose infections were due to Types 3, six or ten organisms developed the disease. Of patients whose primary infection was treated promptly with penicillin 4.5 per cent developed acute nephritis, in contrast to 12 and 23 per cent for untreated and gamma globulin-treated groups respectively. All the patients with acute nephritis recovered completely within eight to ten weeks. Siegel *et al.* (40) described a similar but smaller outbreak in a school population which was also related to Type 12 hemolytic streptococcal infections, and Reed (41) did likewise for an older age school group. The latter author reported that either single (42) or repeated (43) exposures to the nephritogenic strains of streptococci (or filtrates of cultures) produced hypertension, microscopic hematuria and proteinuria in rabbits. Kleinman (44) studied an outbreak of acute nephritis and pyodermia involving 63 children at Red Lake, Minnesota related to a hitherto unrecognized strain of hemolytic streptococci. This strain was characterized by Updyke, Moore & Conroy (45). Subsequently, Reinstein (46) discussed the epidemiologic aspects of this outbreak and demonstrated that mass prophylaxis with single injections of benzathine penicillin aborted the epidemic. Three cases of acute glomerulonephritis also associated with impetigo contagiosa in a family in India were reported by Mukherjee & Ghose (47). Unfortunately, the offending organism was not studied. In contrast, Saslaw & Streitfield (48) in a study of 6400 pairs of throat cultures from 740 school children in

Florida, recovered 187 strains of "nephritogenic" hemolytic streptococci (95 of Type 12, 82 of Type 4, and 10 of the Red Lake type), none of which was associated with attacks of acute nephritis. Likewise, nephritis was not associated with 442 strains of 11 other types.

The association of acute glomerulonephritis with Schönlein-Henoch's purpura is well known. Kreidberg, Dameshek & Latorraca (49) reported 15 cases of purpura in children, all following infections. Three developed acute nephritis some days after the onset of purpura. Jensen (50) reported three cases of Schönlein-Henoch's purpura associated with marked hematuria, apparently due to fish or penicillin allergy. Follow-up in two revealed complete recovery. Wedgwood & Klaus (51) performed follow-up studies in 26 patients two to 15 years after attacks of Schönlein-Henoch's purpura. Blood pressure was normal in all but two (and in these it promptly became normal on bed rest); blood urea nitrogen was normal in all 23 subjects tested, while 12 hr. Addis counts were normal in 16. In ten the Addis counts of erythrocytes, or casts, or both, were abnormal by current criteria, but in only two did protein excretion consistently exceed 100 mg. per 24 hr. Abnormal Addis counts were significantly more frequent ($p < 0.01$) in subjects whose initial attack occurred after the age of six years.

Clark (52) in a review of 265 cases of acute glomerulonephritis found a mortality of 7.5 per cent during the initial attack. However, in recent years the mortality was 3 per cent. Of 178 cases followed for one to 13 years, 75 per cent recovered completely. He commented that no relation existed between the severity of the initial attack and the eventual outcome. Indeed, Kovach (53) reported an inverse relation between increased blood pressure and blood nonprotein nitrogen in children with acute glomerulonephritis. In another study Clark (54) found that the incidence of acute nephritis paralleled overcrowding, presumably resulting in more frequent infections. Akerren & Lindgren (55) observed the effect of early rising in acute hemorrhagic nephritis in 57 children. Alternate cases were kept at bed rest, or were allowed normal activity as soon as gross hematuria cleared. The renal lesion healed in all, and no difference in the rate of healing was noted between the two groups. Unfortunately for the purposes of the study, all were mild attacks, only two having edema and three hypertension. Illingworth, Philpott & Rendle-Short (56), also in alternate cases, studied the effect of severe protein restriction as opposed to ward diets in 42 children with acute nephritis. They were followed an average of two and a half years with a minimum of one year. The rate of recovery of the two groups was similar. On the other hand, Brod *et al.* (57) found that total abstinence from food and water for 60 hr. resulted in prompt improvement in blood pressure, edema and renal functions in 19 of 22 patients whose serum nephrotoxic antibodies disappeared on the regimen, and slow recovery in the other three. No improvement was noted in four patients who did not have antibodies at the onset. Etteldorf *et al.* (58) studied the effect of hydralazine in 24 children with acute nephritis. This drug reduced GFR, RPF and urine flow as well as blood pressure.

It was particularly useful in treating complications such as heart failure, encephalopathy and marked hypertension. In a subsequent study Etteldorf *et al.* (59) found the combined use of reserpine and hydralazine to be more desirable, a single simultaneous administration of the drugs often being sufficient. Less hydralazine was necessary and decreases in renal functions were minimal. Murphy & Murphy (60) found cardiac abnormalities (clinical congestive heart failure, cardiac enlargement or electrocardiographic changes) in 41 per cent of 88 patients with acute glomerulonephritis. Heart failure was usually associated with severe hypertension, and was present in nine of the 16 patients with convulsions. The electrocardiogram was abnormal in all patients with convulsions. Sharpey-Schafer (61) found a "square wave" type of arterial blood pressure response to the Valsalva maneuver in 11 patients with acute glomerulonephritis and increased venous pressure.

O'Dwyer & Montgomery (62) reported three cases of typical acute glomerulonephritis in pregnant women (two in one household due to Type 12 hemolytic streptococcal infections) while Mackie (63) described another. All mothers delivered normal children and made complete recoveries. Werkö & Bucht (64) studied the effects of pregnancy on C_{IN}, C_{CR} and C_{PAH} in 17 women with chronic glomerulonephritis. Thirteen were allowed to go to term. Renal functions were higher during early pregnancy than before pregnancy, late in pregnancy or post-partum. C_{IN} in some patients was considerably reduced. One patient developed acute anuria and three suffered hypertensive toxemia of pregnancy. In all patients renal functions returned to pre-pregnancy values following delivery. The authors concluded that pregnancy did not further injure the kidneys in chronic glomerulonephritis provided renal function was near normal and blood pressure was normal or only slightly increased.

Nephrotic syndrome.—Luetscher, Piel & Curtis (65) have written an excellent review of the nephrotic syndrome while Allen (34) considers its clinicopathologic aspects at length. He introduced a new term, "membranous glomerulonephritis," to designate some of the diseases associated with the nephrotic syndrome. A considerable number of studies on the deranged physiology of the nephrotic syndrome have appeared. Chinard *et al.* (66) found that the change of plasma volume per gm. of albumin retained in circulation following albumin infusions was usually less than would have occurred if the response had been "iso-osmotic." Eder *et al.* (67) collected data on salt and water metabolism and concluded that both glomerular insufficiency and tubular factors played a role in the formation of nephrotic edema. Metcoff *et al.* (68, 69) interpreted their data to suggest that there may be a homeostatic kidney response to a reversible cell defect favoring potassium loss and, indirectly, sodium retention in nephrosis. Gribitz *et al.* (70), however, found that total body exchangeable potassium related to "non-edematous" body weight and red blood cell potassium values was normal in the nephrotic syndrome. Wilcon & Muirhead (71) found a pressor material in blood, ascitic fluid and urine that appeared chemically and elec-

trophoretically to be pitressin, while Luetscher, Dowdy & Harvey (72) isolated crystalline aldosterone from the urine of a child with the nephrotic syndrome. Bruck, Rapoport & Rubin (73), in serial studies on 45 nephrotic children, found that GFR was usually reduced in those who had or subsequently developed evidence of glomerulonephritis, but was normal or above normal in those who never developed evidence of glomerulonephritis. The filtration fraction and the ratio GFR/Tm_{PAH} was decreased in most patients while the ratio RPF/Tm_{PAH} was normal or reduced.

Using labelled glycine Spector (74) showed that the albumin in urine and that in serum were the same in children with nephrosis, while Blahd *et al.* (75), Gitlin *et al.* (76), and Blainey (77), presented evidence of an increased rate of protein turnover, loss of protein in the urine, and body deficit of protein in nephrosis. Rasmussen (78) reported that the half-time of I^{131}-labelled thyroxine in the blood was shorter than normal, that urinary organic iodine was increased and was predominantly thyroxine, that the transport of thyroxine by plasma proteins was normal, and that the peripheral rate of hormone degradation was in the hypothyroid range in patients with the nephrotic syndrome. Sherer & Siefring (79), however, found that protein-bound iodine increased in the serum parallel to the total proteins following prednisone therapy. In normal subjects prednisone decreased serum protein-bound iodine. Randall, Rantz & Rytand (80) found that considerable antistreptolysin O was excreted in the urine of patients with the nephrotic syndrome, which may account in part for the decreased serum values observed in this disease. Cartwright *et al.* (81) observed hypocupremia and hypoferremia in nephrotic syndrome. Hypocupremia was not observed in patients with other hypoalbuminemic states or uremia. The authors suggested that these findings might be the consequence of urinary loss of ceruloplasmin and transferrin. The suggestion regarding ceruloplasmin was confirmed in a subsequent paper from the same laboratory (82). Heidorn (83) found that corticotropin increased urinary ammonia excretion, while Moser & Emerson (84) in a study of phospholipic phosphorus turnover time reported that the specific activity of plasma lipide P in relation to urine phosphates increased more slowly in nephrotic patients than in normals, presumably owing to a delay in attainment of isotopic equilibrium between plasma and liver phospholipides.

Reports on the effectiveness of corticotropin and steroids in the nephrotic syndrome were too numerous to be reviewed individually. Although some preferred short courses of therapy, the majority of reports recommended intensive, prolonged courses. Riley *et al.* (85) recorded a statistical analysis of a co-operative study in a number of clinics of 780 children with nephrosis. The group receiving pre-planned intensive and prolonged hormonal therapy exhibited more effectively improved clinical status and more significantly prolonged lifespans than did the groups receiving sporadic or simply symptomatic hormonal treatment or no treatment at all. The authors did not believe that sufficient data were yet on hand to warrant conclusions con-

cerning the cure rate. Likewise, numerous reports on the effectiveness of malaria in the treatment of the nephrotic syndrome have appeared. Although generally not as effective as hormonal therapy, malaria is probably worth a trial when the hormones fail. Indeed, malaria sometimes caused a remission of the nephrotic syndrome in patients with hypertension and even nitrogen retention [Shaper (86), Gilbertsen & Bashour (87)]. Gairdner & Shute (88) reported complete remissions in 14 and partial remissions in 11 of 51 patients with "pure" nephrosis, and partial remissions in five of 14 patients with "nephritic" nephrosis. Curiously, Keitel *et al.* (89) described an instance of the nephrotic syndrome in a child due to congenital quartan malaria. Rytand (90) recorded the onset of the nephrotic syndrome during a reaction to a bee sting. Nikkila and Gräsbeck (91) discovered no beneficial effects from daily doses of 25 mg. of heparin for one week in five children with nephrosis.

Diabetic glomerulosclerosis.—Root *et al.* (92) pointed out the frequent association of neuropathy, retinopathy and nephropathy in diabetes. They emphasized the importance of the early and continuous diabetic control necessary to prevent these complications. None of 11 patients whose control was excellent for a number of years, and only 2 per cent of 50 whose control was good, developed nephropathy, in contrast to the occurrence of this complication in 28 per cent of 298 patients whose control was poor. Dana & Zubrod (93) reported retinitis in 35 of 45 patients with the Kimmelstiel-Wilson renal lesion, and in 12 of 133 other diabetics. The classic triad of hypertension, proteinuria and edema occurred in less than half the cases. They commented that vascular sclerosis of the kidneys was common. Reid (94), in a study of 104 autopsies on diabetic patients found glomerulosclerosis in 25 per cent, the approximate incidence reported in the other studies reviewed here. Renal arteriosclerosis was absent in only one of the patients with the Kimmelstiel-Wilson lesion. He found that proteinuria in diabetics may occur in the absence of glomerulosclerosis, nor did the absence of proteinuria exclude the renal lesion. Runyan *et al.* (95) reported that amelioration of diabetes was often but not invariably associated with the clinical syndrome of Kimmelstiel-Wilson disease, perhaps because of decreased food intake. However, no difference was noted in daily insulin requirements with the passage of time between those who had and those who had not glomerulosclerosis at autopsy. Epstein & Zupa (96) came to similar conclusions. Other clinicopathologic studies of renal complications of diabetes included that of Lambie & MacFarlane (97) who stated that massive proteinuria in diabetic glomerulosclerosis was usually associated with exudative lesions of the glomeruli, while mild renal lesions were frequently unaccompanied by clinical signs.

Renal vein thrombosis.[3]—The association of the nephrotic syndrome with

[3] *Ed. note:* Two excellent reports concerned with renal vein thrombosis appeared while this chapter was in press (187, 188).

renal vein thrombosis is well known [Blainey *et al.* (98)]. Recent case reports of this combination included an instance associated with polyarteritis nodosa [Miller *et al.* (99)], and one occurring as the terminal event of Bernheim's syndrome [Gray & Laufer (100)]. However, not all instances of renal vein thrombosis were associated with the nephrotic syndrome but occasionally occurred as acute abdominal problems, especially in infants [Traggis & Ellison (101), and Smith (102)] but also in adults [Eikner & Bobeck (103)], and were characterized by hematuria, pain, sometimes a mass in the flank and a fairly typical appearance on intravenous pyelography.

Renal amyloidosis.—Renal amyloidosis may be a complication of several diseases. Sherman *et al.* (104) reported a case with the nephrotic syndrome and uremia secondary to Hodgkin's disease. In a review of the literature for the period 1849 to 1949 they found 40 other cases of renal amyloidosis secondary to Hodgkin's disease. Shuttleworth & Ross (105) pointed out that renal amyloidosis was a not uncommon complication of leprosy and carried a serious prognosis. The average duration of life following the development of proteinuria was 38 months. The mortality was directly related to the degree of renal involvement, but a poor correlation existed between the severity of the leprosy and the renal amyloidosis. In a study of 30 consecutive cases of renal amyloidosis secondary to tuberculosis Wald (106) found heavy proteinuria in 13 but nephrotic edema in only nine. Three died in uremia and only two had hypertension. In two instances some improvement of the amyloidosis followed treatment of the tuberculous process. Despite a postoperative death due to acute renal failure in a patient with evidence of renal amyloidosis Grant & Jones (107) did not consider this complication to be a contra-indication to surgical therapy in view of the poor prognosis of renal amyloidosis and its possible reversion by effective treatment of the tuberculosis.

Renal sarcoidosis.—Hypercalcemia is not a rare complication of sarcoidosis. Scholz & Keating (108) reviewed eight cases complicated by renal disease, calculi being demonstrated in five and nephrocalcinosis in one. Granulomatous infiltration occurred alone or in combination with nephrocalcinosis. Davidson *et al.* (109) reported seven cases of sarcoidosis complicated by hypercalcemia and nephrocalcinosis, while Gleckler (110) observed improvement following cortisone therapy in a patient with generalized sarcoidosis and nephrocalcinosis. On the other hand, Berger & Relman (111) and Cameron (112) described cases in which the renal involvement was mainly the result of granulomatous infiltration. Owen & Henneman (113) reported an interesting case in which renal failure was secondary to complete destruction of the pituitary gland by sarcoidosis.

"Collagen" renal diseases.—Renal manifestations of polyarteritis nodosa are generally the result of small artery involvement. Darmady *et al.* (114), however, described a case in which renal function failure was mainly tubular in origin as demonstrated by functional tests, histologic examination and by microdissection of tubules. Smith (115) studied histologic preparations of

ten cases of systemic lupus erythematosus and concluded that the association of focal necrosis and hematoxyphile bodies in the glomeruli was specific for this disease. Muehrcke *et al.* (116), in a study of 32 patients with systemic lupus erythematosus described the earliest renal lesion as being local glomerulitis including cellular proliferation and occasional fibrinoid deposition. Wire loops were rare. Nephrotic edema associated with low serum cholesterol and cholinesterase carried a poor prognosis. The renal complication of scleroderma was acute and rapidly fatal and was characterized by severe hypertension and uremia secondary to infarcts of the cortex due to fibrinoid necrosis of interlobular arteries and arterioles [Hannigan *et al.* (117)] or to arteriolar hyperplasia and intimal thickening of a peculiar myxomatous character [Bartels *et al.* (118)]. Parkin *et al.* (119) described seven cases of glomerulonephritis, apparently the result of hypersensitivity states, which were characterized by patchy but extensive glomerular lesions including necrosis, proliferation, hemorrhage and crescents, and some tubular changes and foci of interstitial infiltration together with an acute necrotizing alveolitis similar to that described in hypersensitive animals and man. Periarteritis was present in the kidneys of four patients.

Renal disease associated with hematologic disorders.—Reyersbach & Butler (120) and Sturtz & Burke (121) described several families afflicted with congenital hereditary hematuria which was sometimes associated with deafness. The gross hematuria was usually intermittent. The renal lesion in males frequently caused death in uremia at an early age. In females, however, the course of the disease was relatively benign except during pregnancy when toxemia was frequent. In a study of ten adults with sickle cell anemia Etteldorf *et al.* (122) found that GFR, RPF and Tm_{PAH} were greater than normal in early adulthood but that GFR and the ratios of GFR and RPF to Tm decreased with age. Zarafonetis *et al.* (123) found that concentrating ability was considerably impaired in 16 patients with sickle cell anemia and to a lesser extent in 33 subjects with sickle cell trait. They believed that this defect was renal in origin, physiologic or metabolic in nature, and inheritable as part of the sicklemic state. Goldman *et al.* (124) described six patients with sickle cell trait and three with hemoglobin C who had episodes of gross hematuria, often unilateral. Apparently this does not occur in patients with sickle cell anemia. The condition was benign. Sternby (125) studied the kidneys of 108 patients with leukemia, all of whom had proteinuria. Leukemic infiltration occurred in two-thirds, while in 60 per cent the kidneys were enlarged. However, 15 per cent of the instances of enlarged kidneys had no leukemic infiltration. Uremia was present in only two patients and in each was due to a cause other than leukemic infiltration.

The kidneys in endocrine and metabolic disorders.—Reader & Watson (126) described an interesting patient who had recurrent attacks of hematuria, hypertension and nitrogen retention. The attacks began at the midmenstrual period and subsided with the onset of menses. The attacks could be precipitated by estrogens and terminated by corticotropin. Hlad &

Bricker (127) found GFR, RPF and Tm_{PAH} reduced in hypothyrodism and increased in hyperthyroidism. Therapy returned the values to normal in the cases with hyperthroidism while long-term therapy in one patient with hypothyroidism increased GFR despite a further decrease in RPF. The clearance of I^{131} was a linear function of GFR. Yount & Little (128) found decreased C_{IN} and C_{PAH} in seven patients with myxedema. Gershberg *et al.* (129) described a patient with gigantism and acromegaly whose renal functions were 50 to 100 per cent greater than normal and whose kidneys at autopsy were considerably enlarged. Ikkos (130), however, found that GFR and RPF in cases of acromegaly although greater than normal when related to surface area, were normal when related to the volume of extracellular fluid. Although many workers believe that renal insufficiency in gout is secondary to vascular changes and hypertension, several recent reports have presented evidence indicating that the process may sometimes be reversed by uricosuric agents [Phillips (131), Fineberg & Altschul (132)]. Hodges *et al.* (133) found decreased GFR and RFP in four patients with Wilson's disease. Copper clearances were greater than normal and paralleled aminoaciduria. The authors concluded that the renal defect was confined to the proximal convoluted tubules and the renal vascular tree.

Infections of the kidney.—Numerous papers on the treatment of pyelonephritis have appeared in recent years. Kass (134) has written an excellent and informative review on the management of infections of the urinary tract including the use of old and new chemotherapeutic agents. He stressed the importance of estimates of the number of bacteria in the urine. Generally, 10^5 bacteria per ml. urine represented significant bacteriuria. Fortunately, Gram stains of uncentrifuged urine permitted detection of bacteria at just about this level. Beeson (135) likewise stressed the importance of semiquantitative bacteriology in a very thoughtful consideration of pyelonephritis. The hazards of indwelling catheters and unnecessary urologic manipulations were likewise emphasized, as was the etiologic importance of obstructive uropathy. He believed that ascending infection was the most likely route for bacteria to reach the kidneys. Prat (136) measured C_{IN} and C_{Cr} bilaterally in 54 patients and found that the right and left kidneys were affected to different degrees in pyelonephritis in contrast to glomerulonephritis and other renal diseases. Kincaid-Smith (137) found that hypertension in pyelonephritis was related to the severity of ischemic lesions of the kidney noted at autopsy. Brod (138) reported that hypertension was slightly more common when pyelonephritis was bilateral than when it was unilateral. His functional studies revealed greater tubular than glomerular damage. The results of chemotherapy of renal tuberculosis have been very encouraging. For example, Lattimer (139) reviewed his results in a large number of patients. Of one group of 456 patients only three died of uremia. He recommended continuous treatment for one year with the combination of streptomycin, *p*-aminosalicylic acid and isoniazid as being practically 100 per cent effective.

Consequences of renal tubule damage.—Several cases of salt-losing nephritis have been added to the literature [Gjorup (140), Ericson & Svanborg (141), Petersen (142)]. Salt replacement remains the treatment of choice. Etiologies of the renal diseases included pyelonephritis and polycystic disease. A number of additional cases of potassium-losing nephritis have been reported [Evans & Milne (143), Wyngaarden *et al.* (144), Fourman & McCance (145), Sayers *et al.* (146), Mahler & Stanbury (147), Russell *et al.* (148), Eastham & McElligott (149)]. Some of these probably represented Conn's hyperaldosteronism (150), but others were proven to be due to intrinsic renal disease, generally chronic pyelonephritis. Achor & Smith (151), described a case of renal insufficiency secondary to hypopotassemia resulting from diarrhea. Several cases of water-losing nephritis have been described which resembled diabetes insipidus but whose diuresis did not respond to pitressin. Several of these were apparently genetic in origin [West & Kramer (152), Flax (153)] but others were due to organic renal diseases such as hydronephrosis, pyrelonephritis or multiple myeloma [Roussak & Oleesky (154), Morgan *et al.* (155)]. Numerous cases illustrating other defects in the renal tubules have been reported. For example, Luder & Sheldon (156) described three successive generations of a family who exhibited defects in the reabsorption of glucose, phosphate, and amino acids. Lathem, Baker & Bradley (157) studied a patient with Fanconi's syndrome and presented evidence that only a small portion of the nephron population was responsible for the renal manifestations. Tegelaers & Tiddens (158), however, described two children with renal glycosuria and aminoaciduria who not only exhibited impairment of renal function but also the nephrotic syndrome.

Nephrocalcinosis; parathyroids.—Numerous case reports on nephrocalcinosis have been published. Two reviews of the subject [Mortensen & Baggenstoss (159), Mortensen & Emmett (160)] indicated that 75 per cent of the cases were secondary to primary hyperparathyroidism, hyperchloremic acidosis and chronic pyelonephritis, with chronic glomerulonephritis, recurrent renal lithiasis and idiopathic hypercalcemia accounting for the remainder (but cf. section above on renal sarcoidosis). The calcium deposits were mainly in the medulla involving the interstitium, basement membrane of the collecting ducts and the epithelial cells. The reviewers emphasized that they did not consider cases with renal calcium deposits demonstrable only on histologic preparations as nephrocalcinosis. In a study of 147 routine necropsies, Stout, Akin & Morton (161) indeed found a high incidence of microscopic calcium deposits in the kidneys (54 per cent). These were patchy in distribution and were not always bilateral. Nephrocalcinosis is sometimes an inheritable condition as exemplified by the report of Pitts, Schulte & Smith (162). Naylor (163) described a case of nephrocalcinosis associated with hypothyroidism. The report of Kessler (164) on three cases of nephrocalcinosis due to excessive milk and alkali intake is one of several other similar warnings on this hazard. Mitchell (165) described a child with multicystic kidneys who had hypoparathyroidism. He suggested that the

hypoparathyroidism was secondary to hyperparathyroidism in the mother. Bruce & Strong (166) likewise described an infant with hypoparathyroidism whose mother had hyperparathyroidism and nephrocalcinosis. Transplantation of the parathyroid tumor from the mother to child improved the mother but had only transient beneficial effects on the child. Simpson & Wilson (167) described a patient who had nephrocalcinosis and a single parathyroid tumor which was successfully removed. At autopsy four years later the remaining parathyroid showed secondary hypertrophy. Hyperparathyroidism secondary to chronic renal disease is further considered by Karami (168) and Crawford & La Zerte (169).

Cortical and papillary necrosis of the kidneys.—Two cases of cortical necrosis in infants not associated with thrombi have been described, one associated with severe hemorrhagic cystitis [Ali (170)], the other caused by favism transmitted by breast feeding [Casper & Shulman (171)]. Considerable interest in renal papillary necrosis has continued. Christoffesen & Andersen (172) described eight cases, all treated surgically and all surviving, of whom six were cured while two had continued infection. Cates & Hewer (173) likewise described five cases, one due to partial obstruction of the ureter caused by an arterial aneurysm. Swartz (174) reported three cases, two treated successfully surgically.

Renal disease attributable to toxic agents.—Munck & Nissen (175) reported four unusual cases of the nephrotic syndrome apparently secondary to long continued use of mercurial diuretics for heart failure. Glushien & Fisher (176) described a patient with Hodgkin's disease who died following four days of diamox therapy of uremia due to renal lesions identical to those sometimes caused by antibacterial sulfonamides. Foreman *et al.* (177) reported a patient who had acute renal failure due to edathamil calcium-disodium given for plutonium poisoning. The patient recovered, but experimental studies in rats revealed severe hydropic changes in the proximal convoluted tubules. Winter *et al.* (178) described an instance of acute renal failure due to thallium in a child who recovered. Acute renal failure has also been described following neomycin [Powell & Hooker (179)], urethan [Flanagan (180)] and phenylbutazone [Lipsett & Goldman (181), Bruck *et al.* (182), Bolton & Barrie (183), MacCarthy & Jackson (184)]. Reports on radiation nephritis have continued to appear. For example, Grossman (185) reported one case and reviewed the literature.

Epidemic hemorrhagic fever.—One of the outstanding features of epidemic hemorrhagic fever that occurred among the United Nations troops in Korea was an acute renal failure characterized by marked congestion and hemorrhage in the renal medulla. The clinical and pathologic aspects of this unusual renal lesion are discussed in a symposium on the disease (186).

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DISEASES OF THE RETICULO-ENDOTHELIAL SYSTEM AND HEMATOLOGY[1,2]

(The Red Cell and Some of its Problems)

By William H. Crosby, Lt. Col., MC

Chief, Department of Hematology, Walter Reed Army Institute of Research, Walter Reed Army Medical Center, Washington, D. C.

Introduction

As this review was being written Karl Singer died in Chicago. He was one of the great hematologists with an outstanding ability to apply to clinical situations methods being developed in areas of basic research. This made him not only an exceptional clinical investigator but also an outstanding teacher and clinician. Karl Singer was important to American hematology for his discoveries, for the men he trained, and for the concepts that he introduced and advocated. When he came to the United States from Vienna he brought with him important concepts that had escaped notice in this country. The "hemolytic index" is a formula for relating bile-pigment excretion to the amount of hemoglobin in the body. "Symptomatic" hemolytic anemia refers to hemolytic diseases that are secondary to neoplasms, infections, and other "primary" diseases. The very titles of these concepts reflect Karl's lifelong interest in the red cell and its problems. In Boston and later in Chicago he studied the effect of the spleen on the red cell, the pathogenesis of anemia, and the abnormal hemoglobins, always seeking to increase the basic understanding of the diseases with which we as clinicians must cope.

Much of the material on which this review is based reflects the germinal influence of Karl Singer and his ideas. The review itself is intended to reflect his attitude. It deals with his favorite subject, the erythrocyte, a unique and essential organ, and it attempts, as Karl was wont to do, to interpret basic concepts and research in terms of clinical situations and clinical usefulness.

Structure and Function of the Red Cell

Red cell function.—The primary function of the red cell is to serve as vehicle and bodyguard for hemoglobin. Free hemoglobin dissolved in plasma is quickly disposed of: it is oxidized to useless forms or lost through the kidneys and the reticulo-endothelial system. The half-life of free hemoglobin is about 100 minutes (1). Packed into red cells hemoglobin cannot exchange oxygen as quickly as it can in free solution (2), but its normal life expectancy is 120 days (3). The red cell not only retains the pigment but provides protective enzyme systems to prevent its permanent oxidation by the ever-present oxygen (4). The red cell is organized structurally and functionally to

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prevent the hemoglobin from catalyzing its own destruction as it is capable of doing in the presence of unsaturated fatty acids, ascorbic acid, or even glutathione (5).

However, this primary function of red cells is not their only function. They provide 40 per cent of the blood volume; they assist in the transport of CO_2, speeding its conversion to bicarbonate, and back, through the enzymatic action of carbonic anhydrase; they increase the viscosity of blood thereby impeding its flow to permit a more complete exchange of gases and metabolites with each circulation. The red cell also has its own intrinsic functions. Its glycolytic metabolism provides energy for a large number of enzyme systems, most of them concerned with maintenance of the structure and the proper environment within the erythrocyte (6).

Red cell structure (7).—The mature human erythrocyte is a cell without a nucleus. It is disc-shaped, about 100 μ^3 in volume, and one-third of its substance is hemoglobin. The framework of the red cell, its stroma, is composed of protein, lipide and a little carbohydrate. The lipides lie at the surface, oriented with intense polarity, the hydrophobic acids sticking into the outer environment. By reason of this ordered arrangement of the lipide molecules, the red cell carries an intensely negative charge on its surface. The iso-electric point is less than two (8). Because all of the red cells are charged alike, they repel one another, probably with a force so great that their surfaces never touch during the millions of collisions in the blood stream. On the inner surface of the lipide layer there is a correspondingly intense positive charge which would exert a moderate pull on hemoglobin molecules near the surface: at the pH of the blood 7.4, hemoglobin, with an iso-electric point of 6.9, carries a weak negative charge.

The fatty acids of the red cell are complexed with one another and with protein to form a structure that is tough, flexible, and elastic. Most of the framework seems to be concentrated at or near the surface of the cell, but some structural pattern probably extends throughout the entire erythrocyte. Electron microscopic studies of the red cell's surface reveal it to have a granular quality with a few shallow craters, the floors of which are also granular (9). Extremely thin sections, 150 to 300A in thickness, have been cut through unhemolyzed red cells. At magnifications of 190,000 diameters it is possible to resolve objects 60A in diameter, which is the size of hemoglobin molecules (10). Interposed between adjacent red cells there is a thin layer, free of hemoglobin. Although hemoglobin lies within 100A of the surface, the clear zone cannot be interpreted as representing the entire surface ultrastructure of the red cell (11). The stromal framework extends from the surface inward, and the hemoglobin is intimately associated with the stroma. In a sense the stroma supports the hemoglobin, the hemoglobin by its bulk supports the stroma, and the two are somehow bonded together. When pieces are broken from red cells hemoglobin is not lost from either fragment. When a sickle cell opens and closes no hemoglobin is spilled. Hemolysis, when it does occur, is

not the puncturing of a balloon but more likely the dissolution of a bond between hemoglobin and stroma (12).

Hemoglobin structure and function.—The primary function of hemoglobin is the transportation of oxygen. The hemoglobin molecule has the shape of an ellipsoidal sphere, 55×55×65A (13). One can imagine the molecule, shaped somewhat like a goose egg, with four porphyrin rings stuck on the surface like postage stamps (14). An iron atom in the center of each wafer-shaped porphyrin molecule serves not only to fix the porphyrin on the protein, but it is also the point at which oxygen is bound during its transportation. Several points concerning the association of hemoglobin and oxygen are worthy of note. When one heme group has been oxygenated, the hemoglobin molecule is somehow modified and the second and third hemes are more easily oxygenated than was the first. But there is a little resistance to oxygenation of the fourth and last heme. These changes are implicit in the sigmoid shape of the oxygen-saturation curve (15), and they indicate that there is an intramolecular relation between the four hemes. During oxygenation there apparently is a shift in the relative orientation of the heme groups. They move out of positions of relative parallelism, and at the same time the coupling between the heme and the globin becomes stronger (16). This may be of some significance in the orientation of hemoglobin molecules relative to one another as they exchange molecules of oxygen to bring themselves into equilibrium. A system of many hemoglobin molecules is not in equilibrium with 25 per cent of the molecules completely unsaturated and 75 per cent completely saturated; when hemoglobin is 75 per cent saturated each hemoglobin molecule has one free heme.

The hemoglobin molecules within the red cell behave as a system of freely rotating spheres with random orientation and random position (17). The molecules are densely packed: in a red cell of 100 μ^3 there are about 400 million of them. The volume of a single molecule is 83,000A^3, but within the cell each molecule appears to be surrounded by a layer of bound water, into which salt does not penetrate, and which in effect increases the molecular volume by about one-third (13). There is room at the surface of the red cell for only 1 per cent of these molecules; thus the hemoglobin in the center of the cell is separated from the surface by a layer 150 molecules in thickness. With this situation in mind the shape of the hemoglobin molecule appears to have some functional significance. It is conceivable that the spherical molecules, with heme groups on the surface, spin like the inking rollers of a newspaper printing press. Oxygen molecules are passed from one spinning molecule of hemoglobin to the next, moving into the cell or out depending on the oxygen tension in the surrounding plasma. In the capillaries of the lung the red cells become oxygenated in about one second, each of them departing with a complement of 1.5 billion molecules of oxygen. Could the molecules of hemoglobin at the red cell's surface spin fast enough so that each of them could pass along 200 molecules of oxygen in that short time?

One molecule of peroxidase, another heme-protein compound, is capable of reducing 100 thousand molecules per second of peroxide.

Oxygen dissociation.—The oxygen-dissociation curves of red cells, compared with those of hemolysates, are sometimes different in such a way as to suggest that the reactivity of hemoglobin can be modified by its intracellular environment. For example, in anemia the curve may be shifted to the right. The shift of the curve is not caused by any difference in the hemoglobin. When these red cells are lysed the free hemoglobin reacts with oxygen in a normal fashion. The difference is believed to be the result of a slightly lower pH inside the red cells of anemic patients, a condition which favors oxygen dissociation (18). In spherocytosis, however, there is a shift of the dissociation curve to the left (19). It has been suggested that the thickness of the spherocytic cell impedes the unloading of oxygen; however, the points on a dissociation curve do not depend on the rate of equilibration. When the curve is shifted to the left it indicates that the hemoglobin molecules are less reactive regardless of their position in the system. Another explanation should be sought. In spherocytes the glycolytic system is disturbed, and it seems likely that the reactivity of intracellular hemoglobin may depend to some extent upon the integrity of the red cell's metabolic systems. For example, when blood has been refrigerated in citrate solution for a week or more, the oxygen-dissociation curve is shifted well to the left (20). This is not attributable to the formation of abnormal forms of hemoglobin such as methemoglobin. The dissociation curves of hemolysates of such blood are the same as those of fresh blood. When the stored blood is transfused the flaw of oxygen dissociation persists for a day or so but disappears as the damage done to the red cell's metabolic system is gradually corrected in the blood stream of the recipient. The age of red cells may also alter the reactivity of their hemoglobin. Patients with polycythemia vera were treated with a fairly large dose, 6 mc., of radioactive phosphorus in order to suppress erythropoiesis. Two months later it was found that their red cells had a bizarre abnormality of oxygen dissociation compared with the pretreatment curves. At oxygen tensions of 100 per cent, the hemoglobin of the cells could not be completely saturated, and at low tensions the hemoglobin could not be completely unsaturated (21). This may represent a change in aging erythrocytes. Two months after a myelosuppressive dose of P^{32} the blood stream would contain relatively few young red cells. Four months later the abnormality of oxygen dissociation had disappeared. It is a new concept of erythrocyte pathology that metabolic or enzymatic disorders of the red cell may impair its ability to handle oxygen without producing a recognizable change in reactivity of the hemoglobin when it is freed from the cell.

It has long been recognized that hemoglobin of the newborn child has an oxygen-dissociation curve that is shifted to the left. Fetal hemoglobin seems to hold its oxygen more firmly than adult hemoglobin, and this is true of fetal red cells and hemolysates alike. But when hemolysates are dialyzed the dissociation curve becomes the same as that of dialyzed adult hemoglobin

(22). Evidently there is something dialyzable in the environment of fetal hemoglobin that alters its reactivity.

The delivery of oxygen from erythrocytes seems to be controlled with some precision, and in some cases it may be altered to meet the requirements of the subject, as it seems to be in anemia or intra-uterine life. A further example of this is encountered in comparative hematology. Small animals have a higher metabolic rate than large ones. They require more oxygen per gram of tissue, and the dissociation curve of the blood of small animals seems to meet this requirement. It is shifted to the right, which means that oxygen is unloaded in the tissues under greater pressure than it is in larger animals (23). In all animals, great or small, the time required to unload the red cell is probably balanced fairly closely against the brief time available for gaseous exchange. Thus the size of the red cell may be related to the speed with which it must discharge its function, and perhaps for this reason all mammalian red cells are of the same order of magnitude. The red cell of a man is 8 μ in diameter, that of a mouse 7 μ, and of an elephant 9 μ.

Abnormal hemoglobin.—When Pauling found that the hemoglobin of patients with sickle cell anemia (Hb S) had a different electrophoretic mobility from that of normal Hb A, he recognized that the difference represented a genetically determined abnormality of a single sort of molecule, and he proposed the term "molecular disease" (24). Since then other hemoglobins have been discovered and careful comparisons have been made, especially of Hb C, Hb S and Hb A (25). They have the same oxygen-dissociation curves (26). They have the same amino end groups in the globin molecules (27). They have the same dimensions and crystal pattern (28). Differences of mobility during electrophoresis were the means of first identifying the various hemoglobins and these apparently depend upon differences in content of carboxyl groups (29). In addition Hb S appears also to have more free sulfhydryl groups (30). As would be suspected from differences in mobility the isoelectric points of the hemoglobins differ (29). There are also differences in solubility (31), and this difference in particular accounts for the pathogenicity of Hb S. Sickle cell anemia is a serious and progressively destructive disease. An analysis of the damage that is done in these patients indicates that most of it is a direct or indirect consequence of the sickling phenomenon (32). The oxygenated sickle cell is flexible and disc-shaped, but when its hemoglobin is reduced it suddenly opens like a switch knife, pronged and rigid (33). These sickled cells are easily destroyed. They increase the viscosity of the blood and somehow propagate the painful and destructive infarctions which are characteristic of the disease.

Sickling is probably due to a process of gelation (34). The hemoglobin in red cells is a very concentrated solution. Hb S, because of its low solubility, forms a gel more easily than other sorts of hemoglobin (35) and removal of its oxygen reduces its solubility even more. All of these factors combine to provide the proper conditions for the sickling phenomenon in patients with sickle cell anemia. When the cell is deprived of oxygen its hemoglobin forms

a rigid gel. The molecules become oriented on long axes. The stiffening and straightening of these molecular configurations overcomes the pliant fabric of the stroma, and the cell sickles. When the hemoglobin is re-oxygenated it dissolves again, the elasticity of the stroma asserts itself and the normal disc shape is resumed. However, gelation and even sickling are not exclusive characteristics of Hb S. It is an old laboratory trick to suspend normal red cells in a drop of glue to make them sickle (36). The hypertonic solution of a neutral substance removes water from the cell without denaturing its stroma. When the gel point of normal hemoglobin is achieved by dehydration, the cell becomes a sickle.

Paper electrophoresis of hemoglobin solutions is a rapid and cheap substitute for the refined but cumbersome moving-boundary electrophoresis. The use of paper has limitations (37) but it has permitted the screening of large populations in many areas of the world, and as one result, half a dozen new types of human hemoglobin have been discovered. Five were already known: the normal Hb A and fetal Hb F plus three abnormal variants, sickle-cell Hb S, Hb C and Hb D. The new ones, Hbs E, G, H, I, J, K and M, seem to be only moderately or mildly pathogenic. Each of these may occur as a homozygous condition or heterozygous with any of the others and each of the possible combinations represents a different hereditary disease of erythrocytes, an astonishing number of "new" diseases. Only a few of the possible combinations have been reported except, of course, the combinations with Hb A. In combination with the gene for Hb A, these abnormal genes are almost entirely nonpathogenic. Hb CS disease has been encountered in several clinics. Hb DS disease has been reported. Hbs S, E, C have been encountered in combination with the thalassemia gene. The clinical and hematologic aspects of these diseases have been adequately reviewed (37, 38, 39).

These hereditary abnormalities of the hemoglobin molecule, together with thalassemia, which appears to be an inherited abnormality of hemoglobin synthesis (40), are important in several areas apart from hematology. Such cleancut genetic tags are of great value to the geneticist (41, 42). The ethnologist can use the data derived from population surveys to help reconstruct the patterns of prehistoric migrations (43). The epidemiologist is also interested in abnormal hemoglobin. The inheritance of Hb S confers a degree of immunity for malaria (44), an interesting relation between a harmful gene and a harmful infection. When the Hb S gene is present in a population one would expect its concentration to increase in areas where malaria is endemic (because of the immunity) and to decrease where malaria is absent (because it is a harmful gene). This, in fact, seems to be the case (45), and in Africa the selective death rate may be further expanded because of high wastage of life in primitive existence (46). In some tribes the incidence of Hb S is about 50 per cent.

This is not the only hereditary characteristic of the erythrocyte to be associated with modified resistance to disease. The genes that determine blood group in the ABO system seem to be related to the incidence of several

diseases. People of group O, for example, are more likely than other people to develop cancer of the uterus (47), peptic ulcers (48, 49), and diabetes (50). Or it may be said the other way around: people with the A or B gene are less likely to develop these diseases. On the other hand, people of group A are more likely than others to develop cancer of the stomach (49) or oat-cell cancer of the lung (51), and perhaps pernicious anemia, too, since group A is more commonly associated with achlorhydria (49). This suggestion was recently confirmed (49a).

Red cell metabolism.—The metabolism of the red cell is intricate. In this apparently simple bit of protoplasm dozens of enzymes have been identified, and it is not yet known what purpose each of them serves. For example there is probably no turnover of protein in the mature erythrocyte, yet several proteolytic enzymes are found there (52); catalase and cholinesterase are present, and both are fairly active, yet it is not known what they contribute to the red cell's metabolism (53, 54). These are some of the blind spots, but much of the pattern of metabolic activity has been explored (6). Most of the energy for this activity is derived from anaerobic glycolysis; the human red cell converts glucose almost quantitatively to lactic acid. Pathways of glucose oxidation are known to be present, but their quantitative contribution to the production of energy is not great. The enzyme reactions requiring energy are fed from the glycolytic system through compounds such as adenosine triphosphate. ATP serves the red cell's metabolism as a standpipe or storage battery. Adenosine comes to the glycolytic system as a diphosphate and receives a high-energy phosphorylation. The ATP contributes this energy to a metabolic reaction that requires it, and then returns to the glycolytic system to be recharged.

The purposes for which the red cell uses energy are varied:

(*a*) Some energy must, of course, be fed back into the glycolytic system to keep it running.

(*b*) Maintaining gradients across the red cell's surface. The concentration of potassium within the red cell is 100 mEq. per 100 ml., 25 times greater than the concentration in the plasma. It requires energy to maintain this gradient against the tendency of such cations to come into equilibrium. The concentration of sodium, on the other hand, is higher in the plasma than in the cell; it requires energy to keep sodium out. There are other differentials: the concentration of magnesium is higher in the red cell than in the plasma, and calcium is lower. While it is not known what purpose these gradients serve, it is known that they are lowered when glycolysis is interfered with (55).

(*c*) Active transport of materials through the red cell surface. Such substances as glucose (56), phosphate (57) and even potassium (58) do not diffuse altogether passively into the red cell but, at least in part, are handed in by "carriers" that need energy to operate.

(*d*) Turnover of red cell components is a continuing process throughout the lifespan of the cell. Although hemoglobin and, probably, stromal proteins are not replenished (59), there appears definitely to be a turnover of stromal

lipid. Red cell cholesterol is in a state of equilibrium with plasma cholesterol (60), and nonessential fatty acids of the red cell are probably resynthesized continually (61). Glutathione of the red cell is in a very dynamic state with a half-life of four days, and the turnover is probably accomplished by resynthesis (62).

(*e*) The reduction of oxidized cellular components may be thought of as a reparative process. Oxygen is always present and a constant threat: hemoglobin may be oxidized to methemoglobin; the sulfhydryl groups of glutathione may be oxidized and so may the double bonds of unsaturated fatty acids. Glutathione (GSH) is not only synthesized by the red cell, but in order to protect the cell against certain chemical injuries GSH must be maintained in the reduced state. The enzyme, glutathione reductase, is present for this purpose and it derives its energy, not from glycolysis, but from the oxidation of glucose (63). There appears also to be an enzyme "methemoglobin reductase" which serves a similar function in maintaining the integrity of oxyhemoglobin (4). Both of these enzymes require coenzymes to furnish the energy for the reaction, and in both instances there have been recognized "constitutional" diseases in which the red cells are unable to carry out the reduction because of a deficiency of the coenzyme. In "familial methemoglobinemia" there is an adequate amount of methemoglobin reductase but the cofactor is deficient. This, by the way, was the first example to be demonstrated of a disease caused by a specific enzymatic deficiency of the red cell (64). In the red cells of patients who develop hemolytic anemia from exposure to drugs such as sulfanilamide and primaquine, there is a lack of reduced glutathione. This is attributable, not to an absence of glutathione reductase nor lack of the cofactor but rather to a deficiency of the enzyme that reduces the cofactor (65).

Studies of erythrocyte metabolism have had many practical applications.

(*a*) In blood banking the use of citrate as an anticoagulant permitted "indirect" transfusions to be given. (Direct transfusions are without anticoagulant, the blood being given instantly before it has a chance to clot.) Citrated blood could be stored in a refrigerator before it was used, but after several days it began to deteriorate. Then it was found that erythrocytes were glycolytic, and that the period of storage could be doubled by the addition of glucose. During World War II research in this problem was extended and intensified. It was found that the rate of glycolysis was slowed if the blood was made mildly acid, so citric acid was added to the preservative solution. Thus evolved our present ACD (acid-citrate-dextrose) solution with which it is possible to store blood for 21 days before serious deterioration begins to occur. Research on storage of blood has not stopped. In the United States at the present time there is a broad and basic program directed at discovering the causes for deterioration of stored erythrocytes. Every phase of red cell metabolism is under scrutiny, and it is largely because of this program that so much information concerning this remarkable tissue is accumulating so rapidly. The practical application of this latter research has not yet been

realized, but there are indications that it may soon be so. One of the signs of the metabolic deterioration of stored blood is the accumulation of inorganic phosphate and a diminishing rate of glycolysis. It has been recently observed that if ATP is added to stored blood, the evidence of metabolic depletion disappears. The "storage lesion" is reversed (66). It has even been shown that when stored erythrocytes are returned to the blood stream they quickly heal the storage lesion and may then be stored a second time (67).

When the blood is stored in ACD solution to which is added ATP, the blood may be refrigerated for three months and most of the red cells retain their viability—that is to say they can be transfused, and they survive in the circulation after transfusion (68). However, there is a drawback to this procedure. ATP administered intravenously causes an acute fall in blood pressure. To use red cells stored with ATP it is necessary to wash them before they are transfused. To obviate this difficulty it has been proposed that substances other than ATP be used. Several compounds which are chemical cousins of ATP but not so toxic can be used in its place. Results of experiments using desoxyadenosine (68), inosine (69) and guanosine (70), while not so good as those with ATP, still are promising enough to warrant thorough trial.

Another area of basic research on the red cell and methods of prolonging storage encompasses the changes that occur during freezing and thawing. Red cells stored for months at temperatures of −20°C. and lower, have been thawed and successfully transfused (71). For students of erythrocyte metabolism it was of interest to observe that enzymatic activity and metabolic deterioration were slowed but not arrested at −20°C. It requires much lower temperatures to achieve a complete cessation of metabolism in this cell (72). The surface of the red cell seems to be particularly affected by the conditions of storage at −20°C., losing lipides and phospholipides (73). The damage is progressive but at first it is reversible; and constitutes another example of the red cell's ability to heal itself.

The process of freezing and thawing of red cells is technically difficult. As ice crystals form, any salts dissolved in the water are excluded from the growing crystals, and they grow more concentrated in the water that has not yet crystallized. At a certain point the concentration of salt in this as-yet-unfrozen water becomes great enough to denature the stromal lipoproteins and the cell is irreparably damaged. There are two practicable ways to prevent this salt-denaturation. The first is to add glycerin or some other neutral solute to act as a "salt buffer" during freezing (73). The second is to reduce the temperature so rapidly and so low that the cells become solid without crystal formation. This "vitrification" can be accomplished by spraying tiny droplets of blood, 100 μ in diameter, into liquid nitrogen at −195°C. (74). Thawing of the vitrified red cells must be equally rapid, because the crystals will form if warming is slow. Both of these methods are so seriously hobbled by technical difficulties as to preclude their use as practical blood-banking procedures at the present time.

(*b*) The study of red cell metabolism has demonstrated abnormalities that may help to understand the fundamental faults in several erythrocytic diseases. It has been found that the phosphate turnover of sickled erythrocytes of sickle cell anemia is several times slower than that of normal red cells, but there is no difference between normal cells and sickle cells in the normal shape. Sickling also produces a decrease in cellular ATP, diminished incorporation of phosphate into ATP, and an increase of inorganic phosphate. All of these differences indicate that the sickling phenomenon hampers erythrocytic metabolism (75). Studies of the red cells in hereditary spherocytosis indicate that they possess an abnormality of glycolysis reflected in a relatively small phosphate turnover by ATP. Experiments *in vitro* with red cells from different patients with this disease indicate that the faults of carbohydrate metabolism may not be the same in every case (76); at the metabolic level hereditary spherocytosis may not be a single disease. There is reason to suspect that hereditary nonspherocytic hemolytic anemia may also be a "group" of diseases (77). In the reports of paroxysmal nocturnal hemoglobinuria (PNH) there is one undocumented assertion that glycolysis is normal (6), but an isotopic study of phosphate turnover *in vitro* indicates that while the PNH red cells take up less phosphate than normal cells, the turnover of phosphate in the erythrocytic ATP is more rapid (78). In auto-immune hemolytic anemia, spherocytic red cells have been found to have faults of carbohydrate metabolism which are not exactly the same as those in the hereditary spherocyte (79). In PNH and auto-immune hemolytic anemia these faults probably represent acquired abnormalities of red cell metabolism. The erythrocytes of thalassemia major show no abnormalities of glycolysis when examined by the methods which revealed the faults in the spherocytes (6). The significance of this work is not yet clear. This is a diverse group of erythrocytic diseases and the experiments are only exploratory. The similarity of results in different diseases does not indicate identical faults of carbohydrate metabolism.

(*c*) Because erythrocytes can be obtained in large volume without killing or mutilating the donor they are convenient to use as metabolic models. The cholinesterase activity of the red cell has been utilized to study the effects of the so-called nerve gases. These form a group of extremely poisonous organophosphorus compounds that combine irreversibly with cholinesterase and thereby permit the accumulation of acetylcholine. The red cell has no acetylcholine and forms none, and the function of its cholinesterase, which is present in high concentration, is unknown (54). The effects of the nerve gases are studied by providing artificially a substrate for the red cell's enzyme (80).

In the disease hereditary galactosemia there is a congenital incapacity to metabolize galactose. This has been shown to be attributable to a single enzymatic block (81). The conversion of galactose-1-phosphate into uridine diphosphogalactose is normally catalyzed by an enzyme, phosphogalactose-uridine transferase. By studying the red cells of children with hereditary

galactosemia it has been demonstrated that the activity of that enzyme, alone among all those involved in galactose metabolism, is lacking. Galactose metabolism normally takes place in organs besides the red cell, but in these children it does not take place at all. Their erythrocytes provide a model demonstrating a metabolic fault of all the cells normally concerned with galactose metabolism.

An abnormality of glucose metabolism has been demonstrated in the red cells from patients with schizophrenia (82). The addition of insulin to normal red cells *in vitro* causes an increased rate of dephosphorylation of high-energy phosphate compounds. With cells from schizophrenic patients the effect of insulin is reversed: the rate is decreased. The cause of this abnormality and its implications have not been established.

(*d*) Glutathione (GSH) is a chemically versatile substance capable of participating in many kinds of metabolic reactions (83). It is a tripeptide compounded of three amino acids: glutamic acid, cysteine, and glycine. Its chemical reactivity is related to the sulfhydryl (SH) group of the cysteine. GSH is found in many cells including the erythrocyte. Studies with isotopic glycine have demonstrated that GSH can be synthesized *de novo* in the red cell and, further, that the GSH in normal circulating human red cells has a half-life of only four days (62, 84). During the 120 days of the red cell's life the GSH is turned over completely and repeatedly. The experimental interposition of GSH can protect red cells from several kinds of hemolysins such as heavy metals and cobra venom, and the suggestion has been made that, even under normal conditions, GSH may be required to maintain the integrity of the red cell (62). If this were so then the viability of the cell would depend in part upon its capacity to replace GSH and to maintain it in a reduced state.

Even as this speculation was made its validity was being proved by a group of investigators working under the Army Malaria Research Project. During trials of a new antimalarial, primaquine, an amino-benzene compound, it was found that about 5 per cent of Negroes develop an acute hemolytic reaction when given as little as 15 mg. per day of the drug (85). The reaction was essentially asymptomatic. Hemolysis was intravascular with hemoglobinuria and, if the drug was continued, a moderate anemia developed. The investigation which followed this discovery is classical. It was first established by transfusion studies that the fault lay in the red cells rather than in the plasma: in the circulation of a susceptible person his own red cells are destroyed by primaquine, but not those of a nonsusceptible donor (86). Then it was found that only the older red cells are primaquine-sensitive and when the drug is administered indefinitely the anemia disappears. The old red cells have been replaced by young ones (87). During the hemolytic crisis Heinz bodies appear in the primaquine-sensitive red cells (88). Even when exposed to the drug *in vitro* the sensitive red cells develop many Heinz bodies while normal cells have only a few (89). The fact of the injury and the nature of the injury indicate that the primaquine-sensitive

red cells possess a defect in the mechanisms which protect hemoglobin against denaturation (see page 169). Several enzyme systems, glycolysis, catalase, cholinesterase, were examined and found to be normal; but the concentration of GSH in the sensitive cells was 50 mg. per 100 ml. while in normal red cells it was 75 mg. (90). The latest of this remarkable series of investigations has demonstrated a reason for the lack of GSH in these cells (65). The fault was found to be three enzymatic steps removed from the reduction of glutathione. The sensitive red cells have a normal quantity of the enzyme, glutathione reductase, which converts oxidized glutathione to reduced glutathione, and the enzyme functions normally when energy for its reaction is provided by the oxidation of a cofactor, reduced triphosphopyridine nucleotide. The cofactor is present, but the primaquine-sensitive cells are deficient in the ability to reduce it to the active form. Thus the enzyme for preserving GSH is present but the source of energy for its action is obstructed. Finally the fault in primaquine anemia was exactly defined: the cofactor is normally reduced in a reaction which derives its energy from the conversion of glucose-6-phosphate to 6-phosphogluconate, and the enzyme that catalyzes the reaction is glucose-6-phosphate dehydrogenase. In the primaquine-sensitive red cells this enzyme is lacking.

These GSH-deficient cells are sensitive to more than primaquine. They react in the same way to acetanilid, sulfanilamide, thiazosulfone, phenylhydrazine, sulfoxone and phenacetin (91). It is evident that this investigation has not only clarified the problem of primaquine hemolysis but has probably demonstrated the mechanism for many other drug-induced hemolytic crises which have been reported in connection with chemicals of this sort.

Here seems to be an example of faulty maturation of red cells. The young erythrocytes of these susceptible people are normally resistant to primaquine. When the cells are less than 20 days old they are not hemolyzed, but at 50 days they have become quite sensitive (92). As red cells normally mature their enzyme systems change, many becoming inactive (see page 166). In this case a valuable enzyme seems to have disappeared along with those that are normally shed during the process of maturation. The lost enzyme is certainly a useful one but it seems not to be essential, because the faulty erythrocytes survive normally until they are challenged by primaquine or one of its relatives (86). The ability to reduce glutathione is lacking, but perhaps the ability to create GSH *de novo* within the red cell is sufficient protection where there is no challenge.

In sickle cell anemia the concentration of GSH in the red cells is found to be increased. When the cells are deoxygenated and the hemoglobin gels to form the characteristic sickles, GSH is further increased. The reasons for this are unknown, and a clinical application of this information has not been helpful (93). When men are given adrenocorticotropin or cortisone the GSH of the red cells diminishes. To accomplish this diminution several patients with sickle cell anemia were treated with cortisone, and there was a progressive fall of GSH in the blood. The ability of the hemoglobin to gel on deoxy-

genation was considerably diminished. Several patients improved, but others for some reason developed sickle cell crises and the cortisone had to be discontinued.

Production of Red Cells

The normal human erythrocyte is produced in the bone marrow. At first it is a large cell with a large nucleus and intense metabolic activity devoted to manufacturing the proteins of the stroma and hemoglobin. In this discussion the synthesis of these permanent constituents of the mature red cell will be considered in three parts: the protein itself, the porphyrin of the hemoglobin molecule, and iron which is complexed with the porphyrin to form heme. There exists in the red cell some sort of mechanism to balance the effort of this three-pronged assembly line. Although the synthesis of porphyrin and that of globin are quite dissimilar metabolic processes they proceed in step with one another and this synchrony persists even as hemoglobin production dwindles and disappears in the maturing reticulocyte (94). In concert with this the young erythroblasts of normal bone marrow rarely take up more iron than they will require for hemoglobin synthesis (95). In normal erythropoiesis the stromal proteins are formed more quickly than hemoglobin and are completed a little sooner (96).

Protein.—When dietary protein is severely deficient an anemia develops that cannot be corrected by other essential ingredients of erythropoiesis (97). The anemia is normocytic and normochromic, indicating that the erythropoietic reaction to protein deficiency differs in one respect from the reaction to iron deficiency. When iron is in short supply the bone marrow prorates what there is, and instead of producing 100 normal cells with 30 $\gamma\gamma$ each of hemoglobin it may produce 200 cells with 15 $\gamma\gamma$ each. In protein deficiency the number of cells rather than the quality is reduced. The balance between stromal and hemoglobin synthesis seems not to be disturbed; both are hampered to the same extent.

The basophilic quality of the cytoplasm of the erythroblast is attributable to ribonucleic acid, a substance that probably serves as a "template" for the production of proteins. Vitamin B_{12} and folic acid are needed in the synthesis of ribonucleic acid, but no attempt will be made here to describe the complexities of that metabolic cat's cradle. They have been diagrammed in several recent reviews (98, 99, 100). In the presence of deficiencies of vitamin B_{12} or folic acid defective red cells are produced that do not survive normally in the circulation. The defect may reside in the cellular stroma or perhaps in the metabolic machinery. Pernicious anemia red cells are, for instance, somewhat lacking in glutathione (101). A fault in erythroblastic protein synthesis may be reflected also in the abnormally high output of bile pigment. The source of bile pigment is protoporphyrin. In pernicious anemia the production of protoporphyrin is greatly out of proportion to the production of useful hemoglobin (102). This may be interpreted in several ways. The intracellular mechanism that balances the production of heme against the

production of globin may be disturbed, and the excess heme is immediately broken down to bile pigment. Or there may be red cells so poorly constructed that they are destroyed in the marrow or shortly after delivery into the blood, but they do not represent "useful" hemoglobin. Both explanations imply a fault in protein formation. The first implies that globin is formed too slowly or its formation stops too soon. The second implies that the stromal proteins or lipoproteins are inadequate.

Thalassemia is an hereditary disorder of the erythroid tissue characterized by the production of red cells deficient in hemoglobin (40). Because these cells may contain excess amounts of iron and protoporphyrin, along with their lack of hemoglobin, it is suspected that the hypochromia is the consequence of a relative incapacity to synthesize adequate amounts of globin. In patients with this disease the excretion of bile pigment is out of proportion to the production of useful hemoglobin (103).

Protoporphyrin.—The synthesis of porphyrin has been greatly clarified by isotopic methods, and several detailed reviews of these matters are available (104, 105). Porphyrin is a ring-shaped molecule, composed in turn of four pyrrole rings. Altogether the ring structure contains 20 carbon atoms. Additional carbon-atom side chains determine the sort of porphyrin, whether uroporphyrin, coproporphyrin or the useful protoporphyrin which is the pigment found in hemoglobin and the other respiratory pigments.

It is of interest that in the abnormal hemoglobins the protoporphyrin moiety is always normal (24). The abnormalities of hemoglobin and, indeed, the differences between various respiratory pigments such as myoglobin, catalase, and cytochrome, always depend upon the protein moiety. In mature red cells there are, besides hemoglobin, at least two other heme pigments, catalase and methemoglobin reductase.

The raw materials of hemoglobin synthesis are the 4-carbon succinic acid and the 2-carbon amino acid, glycine. A condensation of these two molecules produces delta-aminolevulinic acid, and two molecules of this substance are double-joined to form a compound with a pyrrole ring (106). This monopyrrole is porphobilinogen, the precursor of the porphyrins. Four porphobilinogen molecules are joined to form the tetrapyrrole ring of the protoporphyrin which is incorporated into hemoglobin. The uroporphyrins and coproporphyrins, pigments excreted in abnormal amounts by patients with porphyria, are synthesized through the same chemical pathways as protoporphyrin. It is now evident that these apparently useless compounds are not precursors of protoporphyrin. All three compounds are formed from porphobilinogen through colorless precursors, "leukoporphyrins" (107). In fact, a single leukoporphyrin may be the forerunner of all three (108). Until recently it was suspected that the uroporphyrins were entirely abnormal, found only in the disease porphyria. Their formation after fetal life was thought to be entirely suppressed. Refinements of analysis have, however, demonstrated minute amounts of uroporphyrin in normal urine (109). The metabolic pathways for its synthesis exist in the normal organism, but use of these pathways is al-

most completely interdicted except in porphyria. Clarification of this matter may lead to better understanding of this serious hereditary disease. In "erythropoietic" porphyria there are two series of erythroblasts, one apparently normal, the other characterized by the production of large amounts of porphyrin in the nuclei of erythroblasts. The red cells are short-lived and these patients, as a consequence, may have hemolytic anemia. Splenectomy may relieve the anemia (110). The postsplenectomy increase of nucleated red cells in the blood offers a convenient source of the abnormal erythroblasts for study of the metabolic faults in this disease.

Lead poisoning disturbs hemoglobin synthesis which contributes to the characteristic anemia of that disease. It had been suspected that lead prevented the incorporation of iron into the hemoglobin molecule, thus frustrating its synthesis at the very last step. However, experiments *in vitro* have demonstrated that lead actually interferes with porphyrin synthesis, perhaps blocking the decarboxylation of the leukoporphyrin precursor of protoporphyrin (111). Because of the hemolytic disease that is a part of lead poisoning, the total production of hemoglobin and, as a consequence, the excretion of bile pigment is increased (112). The inhibition by lead within the individual erythroblasts is overbalanced by the participation of a greater-than-normal number of erythroblasts. An increased output of coproporphyrin is also characteristic of lead intoxication, but the reason for this is not known.

Iron.—The incorporation of iron into the molecules is the last step of hemoglobin synthesis (113). Iron for erythropoiesis is carried to the marrow by the plasma and received by the erythroblasts. More than 50 per cent of normal erythroblasts contain small granules of a ferric iron complex which can be stained by the Prussian-blue reaction (114). The young erythroblasts take up more iron from their environment than they can use at the moment for hemoglobin synthesis. The excess iron is stored in granules, and the store is drawn upon as hemoglobin synthesis progresses. By the time the cell is ready for delivery the granules of siderin are gone. Probably less than five per cent of normal erythrocytes contain such granules when they are delivered. When these "siderocytes" reach the circulation the spleen is able somehow to remove the iron granule without destroying the red cell that carries it (95). In diseases of the red cell with an impediment of hemoglobin synthesis such as pernicious anemia, thalassemia and lead poisoning, the "sideroblasts" in the marrow are increased. Iron deficiency anemia is an exception. In that disease hemoglobin synthesis is impaired but there is no iron to spare for making granules (115). The number of sideroblasts is also elevated in many forms of hemolytic anemia, such as hereditary spherocytosis and even acquired auto-immune hemolytic anemia. For some reason these maturing red cells do not utilize all of the iron and as many as 50 per cent of the red cells delivered to the blood may be siderocytes (114). This indicates that young erythroblasts in these diseases misjudge the quantity of iron they need for hemoglobin synthesis and take too much.

Maturation of red cells.—The young reticulocyte retains many of the

metabolic characteristics of the nucleated erythroblast. Some of these persist throughout the lifespan of the red cell and some quickly fade as the reticulocyte matures. The basophilic reticulum substance is ribonucleic acid which is associated with protein synthesis. While this material persists the reticulocyte still is able to synthesize a slight amount of hemoglobin, both the globin and the protoporphyrin (94). The young cell is also capable, to a small degree, of synthesizing ribonucleic acid (116). Oxidative metabolism and the Krebs cycle are both relatively important metabolic pathways in the reticulocyte. But respiration diminishes, and the Krebs (117) cycle disappears in the mature red cell. Many enzymatic reactions dwindle or disappear as the reticulocyte passes into maturity (118). There are changes of other kinds. The reticulocyte is a large cell, it grows smaller, losing some of its surface area and surface lipides as it does so (12). It loses volume, mostly as water, and the hemoglobin becomes more concentrated (119). For the reticulocyte the process of maturation is a diminishing experience altogether.

It has been argued from analogy with other sorts of cells that the erythrocyte might live longer if it retained its nucleus and was thereby able to replenish its enzyme systems. Birds and reptiles have nucleated red cells. The lifespan of nucleated avian erythrocytes is 20 to 40 days (120) and that of turtle erythrocytes, also nucleated, is more than 300 days (121). On the other hand the lifespan of the denucleated red cells of hibernating mammals is three times longer when the animals' body temperature is reduced (122). These observations indicate that a nucleus *per se* does not confer increased longevity on red cells, but a low body temperature is able to do so.

Site of erythropoiesis and delivery of red cells.—The location within the marrow of the site of erythropoiesis has recently been established by thin-section electronmicroscopy (123). For years it has been debated whether or not red cells are produced extravascularly or within special endothelial-lined blood vessels of the bone marrow. Sections of red bone marrow, examined at magnifications of 50,000 diameters, reveal no endothelium inclosing the erythroblasts. Therefore, since erythropoiesis is extravascular the red cells, as they mature and lose their nuclei, must somehow find their way into the capillaries of the bone marrow. This probably does not happen immediately after the nucleus is lost. There is evidence to indicate that the marrow contains a reticulocyte pool, a reserve of young red cells awaiting their time to go into the bloodstream (124). Red cells remain in the reticulocyte stage for about two days, and it is possible that they may spend half of this time in the reticulocyte pool. In event of any sudden demand for red cells these reticulocytes are quickly released and there is a sudden jump in the reticulocyte count of the peripheral blood (125). Control of this release mechanism is a matter of which little is known. The marrow cavity has a limited volume and for every day that the reticulocytes are retained in the marrow, 20 ml. of the marrow cavity must be devoted to house them. In hemolytic anemia two factors compete for space in the marrow. The daily production of red cells is many times increased, and to house one day's production in the reticu-

locyte pool requires 150 ml. of space. At the same time hypertrophy and hyperplasia have driven erythroid tissue into all available marrow space, and probably into space required for the reticulocyte pool. Driven out, the red cells spend less time in the pool and more time as reticulocytes in the peripheral blood, which increases the peripheral reticulocyte count.

Lifespan of red cells.—The lifespan of normal human red cells in the circulation is about 120 days. This has been demonstrated by so many different methods that it is tempting to believe the matter settled (3). There are several careful analyses of the problems involved in the measurement of red cell lifespan (126 to 129). Most of the methods are cumbersome and not adaptable to routine clinical use. But the tagging of erythrocytes with the radioactive isotope of chromium, Cr^{51}, has provided an easy and accurate way to measure the volume of circulating red cells by the isotope-dilution method and, at the same time, to estimate the survival of the tagged red cells by following the decay of radioactivity in the circulating blood. The isotope is added to the blood, *in vitro*, as sodium chromate. During incubation a portion of the Cr^{51} forms a firm chromic bond with hemoglobin in the red cell and the radioactivity remains with the red cell for the rest of its life (129). After transfusion with Cr^{51}-tagged red cells the loss of radioactivity from the blood is somewhat greater than the loss of the red cells measured simultaneously by other methods. The difference, about 1 per cent per day, is usually ascribed to elution of the isotope from the hemoglobin (128), but it might be caused by the older red cells taking up more Cr^{51} than the younger. The Cr^{51} method is especially useful because, unlike P^{32}, the isotope forms a relatively permanent bond with red cell, and, unlike Fe^{59}, it is not re-utilized. Much of it is excreted in the urine. It has almost replaced the Ashby technique of differential agglutination (127) because: (*a*) It is more economical of time. (*b*) It does not require specific antisera. (*c*) It requires only a few ml. of red cells rather than several hundred ml. (*d*) It does not require that the donor red cells be of a blood group different from that of the recipient. The last point is of great importance because it means that a subject can be his own donor, making it possible to study the survival of a patient's red cells in his own circulation. Surveys have been done in many sorts of diseases and much has been done to clarify the role that red cell lifespan plays in the pathogenesis of anemia. In such diverse conditions as cirrhosis (130), chronic granulocytic leukemia (131) and uremia (132), a shortened red cell lifespan has been found.

The measurement of red cell lifespan in the circulating blood is a most sensitive index of erythrocytic disease. Disorders of the red cell are various. They may be structural in nature, or metabolic, immunologic, infectious or even attributable to such physical forces as heat, freezing, ionizing irradiation, and hypotonicity. Whatever the nature of the disease, it manifests itself by shortening the lifespan of the red cells and thereby contributes to the development of anemia. Any anemia must be attributable to a fault of one or both of two factors: the rate of red cell production and the average

lifespan of the circulating red cells (133). When lifespan is shortened the bone marrow may compensate by increasing the output of red cells, and the compensatory ability of the marrow is considerable. In chronic hemolytic anemia, when the bone marrow itself is unhampered by disease, the output of erythrocytes may be eight times the normal (134). A compensatory reaction in the opposite direction apparently is not possible: when the production of red cells is reduced, as it is in aplastic anemia, there is no compensatory prolongation of red cell lifespan. The hibernating mammal provides an exception, for the lifespan of the red cells is prolonged when the body temperature is reduced (122).

Anemia is best defined in terms of red cell mass. In anemia the circulating red cell mass is abnormally small, that is to say less than 25 ml. of red cells per kg. of body weight.

$$\underset{\text{(ml.)}}{\text{Red cell mass}} = \underset{\text{(ml. per day)}}{\text{Red cell production}} \times \underset{\text{(days)}}{\text{Mean red cell lifespan.}}$$

The normal situation, stated in terms of ml. of red cells per kg. of body weight: $30 = 0.25 \times 120$. When anemia is present it is possible, by measuring the red cell mass and lifespan, to compute the output of the erythropoietic bone marrow. Thus it is possible in the various forms of anemia to assess the degree to which each of the two factors, output and lifespan, is at fault (1).

Rate of red cell production.—The rate of red cell production and the rate of destruction are in equilibrium when the red cell mass remains constant in volume (133). The mechanism whereby the red cell mass is held at a constant level is not known. Given a population of red cells with normal lifespan, the size of the red cell mass must be controlled by adjusting the rate of production. In physiologic systems the dynamic steady states, such as body temperature, water balance or red cell mass, depend upon feed-back mechanisms. Mechanical models of these mechanisms are commonplace: when the room temperature falls this information is fed back to the furnace through a thermostat and the heat goes on until the room is the proper temperature again. When the size of the red cell mass shrinks this information is fed back to the bone marrow and red cells are released until the mass is normal, and then the bone marrow is "turned off." All feedback systems depend upon the oscillation of some factor which is capable of producing a stimulation. In the system which maintains the size of the red cell mass it is not known what factor oscillates to cause the stimulation, the red cell volume itself, oxygen tension of the blood, oxygen tension of the tissues, hemoglobin concentration of the blood, total blood volume or the concentration of some end-product of red cell destruction. The amplitude of oscillation may be so small that it cannot be measured by methods now at hand.

It is evident that many factors are capable of modifying the erythropoietic activity of the bone marrow. Chronic hypoxia causes polycythemia; ablation of the pituitary causes anemia. These and similar clinical observations have inspired several investigations. It has been found, for example,

that the plasma of animals made anemic by hemorrhage or hemolysis is capable of inducing polycythemia when injected into other animals (135). A substance has been extracted from the pituitary which is capable of causing polycythemia (136). Although it has been stated that such experiments are concerned with "the fundamental control of erythropoiesis" they probably are not. One should not confuse the mechanism that controls the steady state (a thermostat, for instance) with a mechanism that can modify the level at which the steady state is maintained (adjustment of the thermostat). It is suspected that the "anti-anemic" factors in the pituitary extracts and anemic plasma are of the latter category. Anemic plasma does not increase red cell production in relatively plethoric animals (137). When there is hypoxia of the lower part of the body and normal oxygen saturation of the upper part, including the pituitary and sternal marrow, polycythemia develops with erythroid hyperplasia of the sternal and the iliac marrow (138).

The Destruction of Red Cells

Aging and death of normal red cells.—The aging of the erythrocyte probably determines its lifespan. Physical wear and tear makes little difference. A normal red cell travels 175 miles in its life Red cells of a person with aplastic anemia may travel farther (increased cardiac output) and work harder (increased venous oxygen desaturation) but the lifespan of these red cells is a normal 120 days. The lifespan of the normal red cell seems to be predetermined by the limitations of its metabolic system. From the beginning of its existence as a nucleated cell, the metabolic activity declines by degrees, probably in a logarithmic fashion. When the cell loses its mitochondria and nucleus it loses most of its respiratory capacity, and as it evolves from the reticulocyte stage more of the enzyme systems disappear (118). Throughout its long life in the peripheral bloodstream there is gradual decline of enzymatic activity (139). Several examples of self-repair have been cited above (20, 67, 73); as the enzyme systems decay, the ability of the erythrocyte to repair itself diminishes. When metabolic activity becomes inadequate to maintain the reparative processes, the cell is probably broken and the pieces are removed by the spleen (140).

Pathologic mechanisms of red cell destruction.—The pathologic mechanisms of red cell destruction seem a little more accessible to investigation than the normal because they can often be demonstrated in the test tube with a believable and reproducible scale of hemolysis. In the normal turnover of red cells in the body less than 1 per cent are lost in 24 hours. In the test tube it is possible to hemolyze 15 per cent in 15 minutes and to measure the amount of hemoglobin that is released.

Hemoglobin is capable of reacting with certain types of toxic agents to form Heinz bodies within the red cells (141). These refractile agglomerations of denatured globin, verdohemoglobin and perhaps stromal material (142) are indications of a rather severe intoxication of the cell. Heinz body formation has been aptly described as "granular hemolysis." It is a good example of a hemolytic mechanism active *in vivo* that can be studied *in vitro*. Refer-

ence is made to the discussion of glutathione metabolism above.

Not all drug-induced hemolytic anemias are attributable to the oxidation-reduction reactions that give rise to Heinz bodies. Some patients have developed anti-erythrocytic antibodies when given quinidine (143) or stibophen (144). The antibodies are injurious to red cells only in the presence of the offending drugs plus normal serum complement. The situation is analgous to the mechanism of "sedormid purpura" described several years ago (145).

Complement is also required for hemolysis by the abnormal hemolysins found in paroxysmal cold hemoglobinuria (146, 147) and there is inconclusive evidence that it may be needed by the hemolytic system of paroxysmal nocturnal hemoglobinuria (148). A multitude of normal plasma constituents are involved in this disease: hemolytic factors, hemolytic inhibitors, magnesium, calcium and heparin, and their activity is somehow related to the coagulation system (149). One of the several factors involved in the destruction of the abnormal red cell of nocturnal hemoglobinuria is the globulin which has been purified as "properdin" (148).

In the hemolytic anemias induced by quinidine and stibophen and in paroxysmal cold hemoglobinuria the abnormal hemolytic antibodies are produced by the patient and they are destructive to his own erythrocytes. In both of these diseases, the activity of the hemolysis can be demonstrated *in vitro*, but in most other types of "auto-immune" hemolytic anemia the abnormal antibodies are agglutinins or "incomplete," and they do not provoke hemolysis *in vitro* (150). The mechanism of hemolysis in this sort of anemia has not been fathomed. It has been suggested that incomplete Coombs positive antibodies may not be of primary pathogenic importance (151). It is sometimes possible to demonstrate a normal lifespan of tagged autogenous erythrocytes in a patient with a strongly positive Coombs test. In other cases which seem to fit the clinical criteria of idiopathic auto-immune hemolytic anemia, no auto-antibodies can be demonstrated by any known methods. One such case of exceptional interest occurred in a patient with agammaglobulinemia (152). In his serum there were no demonstrable antibodies of any kind, much less auto-antibodies, and skin tests were negative. He was cured by splenectomy and in his spleen was found evidence of hyperactive phagocytosis. In this patient and in many with auto-immune hemolytic anemia, erythrophagocytosis probably accounts for most of the lost red cells (153). The inability to demonstrate mechanisms of hemolysis *in vitro* may only represent shortcomings of the tests. In some patients with acquired hemolytic anemia and a negative Coombs test it is possible to demonstrate intravascular agglutination (153). The incomplete antibodies, apparently bland *in vitro*, sometimes seem able to fix complement *in vivo* (154).

In about half of the patients with idiopathic auto-immune hemolytic anemia it has been possible to demonstrate "specific" auto-antibodies (151, 155, 156, 157). In such cases the antibodies react selectively with a blood-group antigen on the patient's erythrocytes. Recognition of the specificity of

these auto-antibodies may be of great practical importance. If the patient needs to be transfused it is sometimes possible, by careful matching, to select a donor whose red cells do not contain the specific antigen. The donor's blood group would, of course, be different from the patient's, but the use of such blood may provide red cells which could survive and function where the patient's own are destroyed (157).

From a theoretical point of view, the demonstration of specificity in the so-called auto-antibodies favors the concept that these globulins are true antibodies and not indiscriminate tissue-injuring globulins, or nonspecific globulins that fasten onto red cells already injured.

The concept of auto-immune disease is gradually broadening. The auto-antibodies are known to injure platelets and white cells as well as red cells. In some patients they injure all three (158). It has been suggested that they also act against the marrow (159) and blood vessel walls (160), and that cirrhosis may sometimes be caused by auto-antibodies that damage liver cells (161).

Disposal of red cells.—When the erythrocyte has been destroyed its iron and protein are reutilized, but the porphyrin is excreted as bile pigment (1). From the site of hemoglobin degradation the pigment is transported in the plasma as bilirubin, bound to albumin (162). This form of bilirubin is insoluble in water and it will not react in chemical tests until it is dissolved in alcohol; it is the so-called indirect-reacting bilirubin. It is cleared from the plasma by the liver, and there it is complexed with glucuronic acid and is thereby converted to the water-soluble direct-reacting bilirubin (163). This bilirubin is excreted into the bowel where it is reduced to stercobilinogen and similar compounds, lumped together as urobilinogen (164).

Bilirubin clearance.—Rate of bilirubin clearance by the normal liver has been derived by calculating the rate of pigment formation and measuring its concentration in the plasma. The lifespan in plasma of the indirect-reacting bilirubin is about 100 minutes where liver excretory function is unimpaired (1). This is true of both normal subjects and patients with chronic hemolytic anemia. The patient's hemolytic jaundice is not caused by a "sluggish liver." In hemolytic anemia without liver disease one does not encounter plasma bilirubin concentrations in excess of 4 mg. per 100 ml. This is about seven times the normal concentration, but the rate of hemolysis is also about seven times normal. These figures for hemoglobin destruction and the bilirubin level in the plasma match fairly well, but the matching may be coincidence. When a massive quantity of useless hemoglobin is injected it will be destroyed. Regardless of the amount of hemoglobin injected, the plasma bilirubin does not rise above 4 mg., but it may remain at that level for several days until all of the pigment is disposed of (165). The system for converting hemoglobin to bilirubin is apparently limited to handling about 50 gm. of hemoglobin per day.

The amount of bile pigment produced each day is related quantitatively to the amount of hemoglobin that is destroyed: 35 mg. of bilirubin from

each gram of hemoglobin. When the rate of hemolysis is known it is possible to compute an anticipated amount of bile pigment that might be recovered. The actual recovery usually falls short, for some of the pigment is diverted or destroyed in the process of excretion. But sometimes the recovery is greater than the anticipated amount, which indicates that the hemoglobin of circulating red cells is not the only source of bile pigment. The existence of such sources has been demonstrated by isotopic methods (166), but it is not yet known where they are, or whether immature red cells are destroyed in the bone marrow (103) or heme synthesized by organs such as the liver (167). Porphyrin compounds, other than heme, such as uroporphyrin and coproporphyrin, are not excreted as bile pigments (104).

The existence of an hiatus between the anticipated and the actual recovery of bile pigment indicates that the measurement of fecal urobilinogen provides only a rough idea of the rate of hemolysis (102, 103, 133). It is largely for this reason that in clinical practice this method of studying hemolytic disease has been supplanted by the direct measurement of red cell survival.

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NUTRITION AND NUTRITIONAL DISEASES[1]

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The last half century has brought great advances in knowledge concerning human dietary requirements. That the application of this knowledge has, in many parts of the world, fallen far short of eliminating disease attributable to the lack of specific essential nutrients is abundantly attested by the reviews of recent years in these pages as well as by a steady stream of current literature [Sure (1), Pollack (2), Jolliffe & Ta-Cheng (3), Waterlow (4)]. However, in a few countries, including our own, this advancement of knowledge has co-operated with economic prosperity to bring about marked reduction in the incidence of classical nutritional "deficiency" diseases. Rather than diminishing the importance of nutrition in medicine, this change has produced a shift in focus of interest. Whereas major emphasis had been given to the medical effects of inadequate intake of one or more nutrients, now more and more attention is being given to the effect of disease processes on the ability to utilize nutrients, and to factors which alter or, as the term has come to be applied, "condition" the requirements for a nutrient.

This review makes no attempt to cover all of the literature of the past year in the field of nutrition. It has the more modest aim of surveying a few topics in the area of nutrition in which important advances have recently been made.

Nutrition and Liver Disease

Experimental fatty liver produced by dietary alterations.—Just at the time when the confusion is being dispelled concerning the factors involved in the production and prevention by dietary means of experimental liver necrosis and fatty liver with cirrhosis (5), a new form of dietary hepatic injury has been recognized. It is now rather clearly established that diets low in protein or containing poor quality protein may produce fattiness of the liver even when adequate amounts of choline and methionine are present [Best *et al.* (6), Shils *et al.* (7), Harper *et al.* (8)]. The fat accumulation in this condition is principally in the periportal portion of the liver lobule in contrast to its centrolobular localization in choline deficiency. The first observations on this phenomenon were made by Elvehjem and co-workers (9, 10) who were studying weanling rats on low casein diets deficient in niacin and tryptophan. The addition of these substances improved the rate of body weight gain but actually caused an increase in liver fat. The addition of gelatin prevented the accumulation of fat in the liver and threonine was as effective as gelatin (11). With diets containing crystalline amino acids as the sole source of nitro-

[1] The survey of literature pertaining to this review was completed in July, 1956.

gen, the liver fat content varied with the amount of threonine in the diet (12). However, when low protein rations were prepared from sources other than casein, the effectiveness of threonine varied, indicating that other amino acids were involved (13). The delicacy of the balance of amino acids required for maintenance of normal fat levels is indicated by the observation that the addition of 0.1 per cent methionine to a basal ration containing 9 per cent casein increased liver fat markedly (14). Thus a lipotropic agent, methionine, is, in this situation, actually lipogenic, further demonstrating that these fatty livers are etiologically distinct from those seen in choline deficiency.

The potential practical significance of amino acid imbalance is apparent when the diet contains rice as the sole source of protein. A marked weight response occurs when lysine and threonine are added, but the level which produces this effect does not prevent liver fattiness. When lysine is increased to the point at which fat accumulation is suppressed, depression of weight gain occurs (15). This in turn can be prevented by increasing the levels of leucine, isoleucine, valine and histidine (16).

Shils and co-workers (17) ranked the amino acids according to their ability to prevent fatty livers in rats subsisting on diets in which the protein was derived from cornmeal, rice, or cassava. Tryptophan and lysine, alone or together, partially or completely prevented the fatty condition. Threonine had no effect. These authors also emphasized that the amino acid requirements for weight gain and for prevention of fatty liver are quite different.

Benton *et al.* (18) studied the effect of different dietary fats on liver fat deposition. The fats were fed at a level of 20 per cent in a low protein (9 per cent casein) diet. Butter and lard resulted in much higher liver fat levels than did corn oil or margarine. This effect was increased by decreasing the choline or protein content of the diet, indicating that this action of fat occurs with both the choline-deficiency and the low-protein types of fatty livers. The content of saturated higher fatty acids is believed to be the determining factor in the differences between the various fats; this is borne out by the finding that stearic, but not oleic, acid reproduced the effect.

Nitrogen metabolism in liver disease.—Increasing attention is being given to the abnormalities in nitrogen metabolism which occur in liver disease. Plough and co-workers (19) studied nitrogen balance in patients with viral hepatitis and concluded that these patients appeared to be able to retain nitrogen as efficiently as normal persons. In patients with hepatic cirrhosis Gabuzda & Davidson (20) demonstrated that stool nitrogen excretion was not increased above normal over a range of protein intake of from 0 to 100 gm. daily. They also found that urinary nitrogen excretion was normal under conditions of minimal nitrogen intake, indicating that catabolism of endogenous nitrogen was not accelerated. The protein intake required for nitrogen equilibrium was 56 gm. per day in those with the highest requirement and was considerably less than this amount in most of the patients. In patients

with severe hepatic cirrhosis maintained on a constant diet for 40 to 50 days, a progressive decrease in urinary excretion of nitrogen occurred concomitantly with clinical and laboratory improvement, signifying that the efficiency of utilization of nitrogen increased with improvement in the disease. Plough and co-workers (21) showed that supplements of fat and carbohydrate spare nitrogen and that the amount of nitrogen spared per added calorie is directly related to the level of protein in the diet.

In recent years a number of reports have appeared which indicate that the levels of amino acids in blood and urine may be elevated in patients with liver disease. Recently Wu and associates (22) studied the concentration of free amino acids in the plasma of patients with hepatic coma. Among 12 patients studied, glutamic acid, glutamine and tyrosine were found to be increased in nine, methionine in seven, and glycine in two. There was no consistent pattern in the relation between elevation of individual amino acids and severity of coma. Walshe & Senior (23) made an extensive study of cystine metabolism in patients with liver disease. The polarographic method employed measured both cysteine and cystine. Increased levels in both plasma and urine were found, but renal clearance of the substance was normal. Oral administration of cysteine gave a markedly abnormal blood tolerance curve in all patients with liver disease.

The precipitation of hepatic coma in some patients with liver disease by the administration of various nitrogenous substances, including protein, and the possible relation of blood ammonium to this phenomenon is an active field of inquiry [Bessman (24), Schwartz (25)]. The methods for determining blood ammonium vary considerably, and there is lack of agreement as to whether the methods measure preformed ammonium or ammonium formed after the blood is shed [Calkins (26)]. All investigators have found the blood ammonium to be elevated in the majority of patients with hepatic coma but most have failed to find a correlation between degree of elevation and depth of coma. Bessman & Bessman (27) studied arterial, cerebral venous, and peripheral venous ammonium levels. They found elevation of both arterial and venous ammonium levels roughly paralleling depth of hepatic coma. Coma from other causes was not accompanied by elevated ammonium levels. Arterio-venous differences revealed that both brain and peripheral tissues take up ammonium at a rate proportional to arterial level. They hypothesize that elevation of ammonium may cause coma by siphoning off alpha ketoglutarate to yield glutamate and thus depress oxidation in the citric acid cycle.

White and co-workers (28) have made an exhaustive study of ammonium tolerance in liver disease. By hepatic vein catheterization they found that the abnormally elevated peripheral blood levels of ammonium after oral administration of ammonium chloride to patients with liver disease was usually caused mainly by portal collateral circulation diverting the portal blood with its high ammonium content around the liver. However, in ad-

vanced liver failure the inability of the liver to metabolize ammonium normally also contributed significantly.

Attempts to treat hepatic coma by administration of sodium glutamate, on the hypothesis that this might depress the elevated blood ammonium levels, have been unsuccessful [Alexander *et al.* (29)] or equivocal [Webster & Davidson (30)]. In rats du Ruisseau and co-workers (31) found that arginine afforded protection against a lethal challenge of ammonium acetate and that this was associated with suppression of the rise in blood ammonium. A number of other substances including sodium glutamate and alpha ketoglutarate did not protect. The effect of arginine is presumably due to acceleration of urea formation from ammonium in the Krebs-Henseleit cycle.

Phear and co-workers (32) believe that the induction of hepatic coma in susceptible patients by feeding methionine is not attributable to ammonium intoxication. They suggest that conversion of methionine to a toxic substance may be accomplished by intestinal bacteria. Oral administration of chlortetracycline prevented or delayed the methionine toxicity without depressing blood levels of either ammonium or methionine.

Dietary treatment of human liver disease.—The final report of the Hepatitis Study Team on the treatment of viral hepatitis during the Korean conflict has now appeared (33). In this large and well controlled study, it was found that patients forced to eat a diet supplying an abundance of calories, protein, and vitamins improved more rapidly than did patients who ate only as much as they chose of a regular hospital diet. It was further observed that the duration of hepatitis was shorter in those patients forced to eat a diet containing 19 per cent of calories as protein than in those consuming 11 per cent of calories as protein.

A well-reasoned evaluation of the literature dealing with the efficacy of lipotropic agents in the treatment of fatty cirrhosis has been prepared by Gabuzda (34). He states that there is no conclusive evidence that choline exerts a specific therapeutic effect in patients with fatty cirrhosis of the liver associated with alcoholism, or that supplementing an adequate diet with choline, methionine, other lipotropic agents, or vitamins brings about a more complete or more prompt recovery than does diet alone. Mindrum & Schiff (35) treated eight patients with severe fatty liver with a diet containing 4300 calories, 110 gm. of protein and 310 gm. of fat. In spite of this high fat intake, fat disappeared from the liver as determined by biopsy, and the patients improved clinically. Barros and co-workers (36) treated seven patients with portal cirrhosis and ascites with a rice diet which provided 20 gm. of protein and 200 mg. of sodium daily. All of the patients showed marked clinical improvement with disappearance of ascites, improvement in serum protein level and elevation of hemoglobin. Some of these patients had failed to respond to a diet containing 100 gm. of protein and 900 mg. of sodium. Davidson (37) also emphasized the importance of long-term sodium restriction in the management of cirrhosis with ascites. He found however, that

once the ascites had subsided, increased sodium intakes could often be tolerated without recurrence of ascites. Talso and co-workers (38) have shown that the edema and ascites in patients with cirrhosis represent an isotonic expansion of extracellular fluid in contrast with the hypotonic expansion of intra- and extracellular fluids in heart failure. Furthermore, they found that the tendency to increased extracellular fluid volume exists before edema and ascites are seen and persists after these have responded to treatment, indicating that a fundamental defect in water and sodium metabolism is present in these patients.

Amino Acid Requirements of Human Subjects

Several extensive series of studies on the minimum amount of individual amino acids required to achieve nitrogen equilibrium in human subjects have recently been completed [Rose *et al.* (39), Leverton *et al.* (40 to 44) Swendseid *et al.* (45, 46)]. The results of these are summarized in Table I.

TABLE I

Amino Acid Requirements for Nitrogen Equilibrium

Amino Acid	Requirement, grams per day		
	Rose *et al.**	Leverton *et al.*†	Swendseid *et al.*‡
Tryptophan	0.15–0.25	0.08–0.16	0.15
Lysine	0.40–0.80		0.90
Threonine	0.30–0.50	0.10–0.31	0.35
Leucine	0.50–1.10	0.17–0.62	0.70
Isoleucine	0.65–0.70		0.35
Valine	0.40–0.80	0.38–0.64	0.60
Phenylalanine	0.80–1.10§	0.12–0.22¶	1.15#
Methionine	0.80–1.10‖		0.65**

* Young adult males.

† Young adult females.

‡ Young adult females; requirements for individual amino acids were determined only for isoleucine and cystine plus methionine; the mixture listed sustained nitrogen equilibrium in each of six subjects.

§ Tyrosine was able to spare 70 to 75 per cent of this requirement.

‖ Cystine was able to spare 80 to 89 per cent of this requirement.

¶ With 900 mg. of tyrosine in diet.

0.25 gm. phenylalanine plus 0.90 gm. tyrosine.

** 0.45 gm. cystine plus 0.20 gm. methionine.

It will be noted that the requirements are consistently lower in female than in male subjects. Rose & Wixom (47) found that a total intake of 3.5 gm. of

nitrogen per day with 1.4 gm. coming from essential amino acids, was capable of supporting nitrogen equilibrium. Holt and associates (48, 49) reported that in infants one to six months of age the requirement for phenylalanine was 90 mg. per kg. per day and for threonine 60 mg. per kg. per day. Allison (50) has emphasized that amino acid requirements will vary significantly with other dietary factors, physiological states, and environmental influences.

Effect of Diet on Serum Cholesterol Levels

Because of its possible relationship to human atherosclerosis the effect of various factors on serum cholesterol level in human subjects is under continuing intensive investigation. Keys and co-workers (51) were the first to point out the influence of dietary fat intake on serum cholesterol levels. In the most recent of their series of studies on men in various parts of the world, these investigators (52) have confirmed their earlier findings; namely, that in healthy young men the serum cholesterol level is substantially independent of dietary composition whereas in middle-aged men serum cholesterol levels are higher in those who consume a diet high in fat. The earlier laboratory studies seemed to indicate that this effect of dietary fat on serum cholesterol level was essentially the same for fats of vegetable and animal origin [Keys *et al.* (51, 53), Hildreth *et al.* (54), Mayer *et al.* (55)]. However, in the past several years evidence has been accumulating which indicates that, at least under some dietary conditions, highly unsaturated fats of vegetable and marine origin may, when added to the diet, lower rather than raise the serum cholesterol level [Beveridge *et al.* (56), Kinsell *et al.* (57, 58, 59), Ahrens *et al* (60), Bronte-Stewart *et al.* (61)]. The conditions required for producing this effect and the mechanism of it remain to be elucidated.

Obesity

The recognition of obesity as a major nutritional problem is reflected in the abundance of current literature on this topic (62, 63). Although the therapeutic problem in obesity would appear to be a straightforward one, the continuing appearance of recitals of failure in the majority of patients on supervised dietary programs followed for long periods demonstrates that there is no reason for complacency in this field [McCann & Trulson (64), Young *et al.* (65)].

Regulation of food intake.—A symposium on the regulation of hunger and appetite (66) revealed little agreement among experts on basic mechanisms but did indicate that investigators in this field are giving major emphasis to the role of the central nervous system and to metabolic interrelationships. The glucostatic theory of regulation of food intake [Mayer (67)] continues to occupy the center of the stage, and the evidence bearing on it continues to be conflicting. Stunkard and his associates (68) found that injection of glucagon into human subjects produced elevation of blood glucose with in-

crease in arterio-venous glucose difference which was temporally correlated with inhibition of gastric contractions and subsidence of the sense of hunger, all in keeping with the glucostatic theory. Fryer and associates (69), on the other hand, were unable to correlate arteriovenous glucose differences with satiety in subjects on various reducing diets. Bernstein & Grossjan (70) found that intragastric or intravenous administration of glucose did not suppress food intake or the report of desire to eat in their human subjects. Mellinkoff and co-workers (71) reported that the suppression of appetite after ingestion or infusion of amino acids was negatively correlated with serum amino acid concentrations but bore no constant relation to blood sugar level.

In experimental obesity in animals a number of abnormalities of eating behavior have been described (63). Hollifield and co-workers (72) found that mice with gold thioglucose obesity do not respond to starvation with increased running activity as do normal mice, whereas mice with the hereditary obesity-diabetes syndrome were normal in this respect. In genetically obese mice Fuller & Jacoby (73) reported, as compared with normal mice, a lessened ability to adjust food volume upward when the nutritive density of the diet is decreased by dilution with inert agents, a greater decrease in food consumption when bitter additives were present, and an increase in nutritive intake when the fat content of the diet was increased.

Caloric intake of obese persons.—There is essentially complete agreement among authorities that obesity results from an excess of caloric intake over caloric expenditure (74). Furthermore, it is generally assumed, perhaps gratuitously, that the caloric expenditure of obese persons is normal and that the imbalance is entirely due to excessive intake. Although there are many reports in the literature dealing with estimated caloric intake of obese persons, these give conflicting views (see Beaudoin & Mayer (75) for review of literature). There had been some evidence [Fry (76), Peckos (77)] to indicate that obese persons may actually consume a significantly smaller number of calories per day than non-obese persons of the same height and age, and recent studies offer some confirmation. Johnson and co-workers (78) studied 28 obese and 28 non-obese high school girls matched for height and age. The obese girls consumed an average of 2000 kcal. per day, the non-obese 2700 kcal. per day. Analysis of activity records showed that on the average, the obese girls were significantly less active.

The role of inactivity in the genesis of obesity was supported by another study conducted by Mayer *et al.* (79) on millworkers in West Bengal. Caloric intake was found to vary directly with physical activity only when total activity was above a threshold level. Below that level a decrease in activity was accompanied by an increase in food intake. Body weight showed no correlation with activity in the normal activity range, but in the sedentary range body weight varied inversely with activity. These findings were strikingly similar to those obtained in an earlier study by Mayer and associates (80) on rats subjected to graded amounts of exercise.

Another study showing an inverse relation between body weight and

caloric intake was reported by Swanson and co-workers (81). Women between the ages of 30 and 90 years were the subjects, and it was found that the intake of those within 10 per cent of ideal weight was 1810 kcal. per day whereas those 20 per cent or more above ideal weight consumed 1650 kcal. per day. Grossman & Sloane (82) studied the body weight, body fatness (as calculated from skinfold measurements) and caloric intake of a group of soldiers. Statistical analyses revealed that caloric intake varied inversely with body fatness independent of body weight, i.e. caloric intake decreased as per cent body fat increased. This relation was found to exist both during a period of *ad libitum* activity and during a period when the men adhered to a schedule of moderately severe activity.

The delineation of the interrelationships between body weight, body fatness, activity and caloric intake presents some difficult problems. One must take into consideration whether body energy stores are constant or changing during the period of observation. However, the studies reported above are sufficiently consistent to indicate that it is not safe to assume that obese individuals invariably consume more calories than do non-obese ones. It would be particularly interesting to obtain information on the caloric requirement of obese persons after their body weight had been reduced to normal.

There is a need for extensive studies of food intake and energy expenditure in obese subjects as compared to normal persons. It is often assumed that the measurement of caloric intake can be accomplished with great accuracy. However both the estimation of the amount of food eaten [Hollingsworth (83)] and the assessment of the energy value of that food [Widdowson (84)] present problems which have not received serious attention since our present systems for estimating caloric intake were established by the Atwater school 60 years ago.

Important advances have been made in the techniques for measuring energy expenditure. By the combined use of light-weight, portable metabolimeters and time-motion studies, total energy expenditure during long periods when subjects are engaged in their normal activities can be estimated with good accuracy [Wolff (85), Edholm (86), Passmore (87), Edholm *et al.* (88), Garry *et al.* (89)]. Long term measurements of total energy expenditure have been accomplished by isotope dilution methods in mice [Lifson *et al.* (90)] and the application of these to human subjects may become feasible. Passmore & Durnin (91) have performed an estimable service by compiling the world literature on the energy cost of various tasks. Of particular interest in regard to energy balance in obesity is the finding of Miller & Blyth (92) that the caloric cost of activity involving moving the body (walking) is a function of body weight and is independent of obesity.

Fat metabolism in obesity.—Radio-isotopic studies have demonstrated certain differences in fat metabolism in various experimental forms of obesity [Mayer *et al.* (93 to 96)]. The incorporation of acetate into fatty

acids is depressed by fasting in normal animals and in those with gold thioglucose and hypothalamic obesity, but in mice with the hereditary obese-hyperglycemic syndrome, the rate of incorporation of acetate into fatty acid is greatly increased and is not depressed by fasting. During *ad libitum* feeding the amount of endogenous fat burned per day is decreased in all three forms of experimental obesity, but this is most marked in the hypothalamic form. Parson & Crispell (97) found that the respiratory excretion of labelled carbon dioxide per gm. of body weight after injection of labelled acetate was the same in obese and non-obese littermate mice, thus failing to confirm an earlier study by Guggenheim & Mayer (98) who reported depression of acetate oxidation in the obese animals.

It has been known for some years that the rate of increase in body weight is correlated with the fat content of the diet under some experimental conditions [Deuel (99)]. Recently Fenton and co-workers (100,101) showed that this increased weight gain resulted from obesity in the sense that the percentage of fat in the carcass was increased. These workers studied four different genetic strains of mice and found that all four strains increased their caloric intake when placed on a high fat diet but that in only two of the four strains was this reflected in an increase in body weight. Subsequent studies revealed that the strains which did not become obese showed an increase in oxygen consumption with the increased caloric intake, whereas the strains which became obese did not show increased oxygen consumption and presumably deposited the extra calories as fat rather than burning them. Mickelsen, Takahaski & Craig (102) fed diets containing 85 per cent of the calories in the form of fat and found that obesity resulted in each of three different strains of rats. The possibility that the fat content in the diet may play a role in the production of obesity assumes considerable practical importance when it is recalled that the average American diet provides approximately 40 per cent of calories from fat [Keys (52)]. The striking difference in the effects of saturated and unsaturated fatty acids on serum cholesterol levels and on liver lipide accumulation suggests that the role of this factor be studied in relation to obesity.

Composition of obesity tissue.—Obesity is best defined as excessive accumulation of fat in the body (103). The question arises as to whether accumulation of excess fat is accompanied by increments of protein and water. One approach to this question comes from the study of various forms of experimental obesity in animals, in which the entire carcass can be analyzed chemically. Mayer and associates (104) studied animals made obese by three different experimental procedures; genetic selection, hypothalamic lesions, and injection of gold thioglucose. In each of these types of experimental obesity these workers found that over 90 per cent of the extra body weight of the obese animals, as compared with their non-obese controls, could be accounted for by fat. There was no significant increase in protein and only a small increase in water. In confirmation of this finding, van Putten *et al.*

(105) compared the carcass composition of rats with hypothalamic lesions to that of unoperated control animals with which the operated animals had been pair-fed. Under these conditions, the animals with hypothalamic lesions did not gain more weight than the unoperated controls, but their carcasses contained considerably more fat, less water, and slightly less protein. The results of the studies of Alonso & Maren (106) on mice with hereditary obesity are similar. The obese mice weighed approximately twice as much as their non-obese litter mates and approximately 70 per cent of the weight gain could be accounted for as fat with water comprising most of the remainder. No increase in protein was found. These same workers found that when, by restriction of food intake, the obese mice were held to the same body weight as the controls, their carcasses still contained two to four times as much fat with corresponding decrements of water and protein. The only studies of experimentally obese animals in which a portion of the weight gain has been found to consist of protein are those of Waxler and co-workers (107, 108) on mice with obesity following gold thioglucose injection. As much as 10 per cent of the weight gain was attributable to protein. No explanation is available for the discrepancy between the results of Waxler and those of Mayer on the protein content of carcasses of animals made obese by injection of gold thioglucose.

In prescribing diets for obese patients it is generally assumed [e.g. Rynearson & Gastineau (74)] that the excess tissue which will be lost during caloric restriction is composed principally of fat (80 to 90 per cent) with water constituting the remainder. From this assumption, which is based upon analyses of adipose tissue, it is calculated that the caloric value of the weight loss is 3500 kcal. per pound or 7700 kcal. per kg. Some attempts have been made recently to obtain more direct evidence on the caloric value and composition of gains and losses in body weight in human subjects. Keys, Anderson & Brozek (109) studied men before and after they had gained weight as the result of simple overeating. By measuring the density of their bodies by underwater weighing and the extracellular water volume as thiocyanate space, they calculated that about 62 per cent of the weight gain was fat, about 14 per cent extracellular fluid, and the remainder was assumed to be "fat-free cells" containing approximately 20 per cent protein. Thus the "obesity tissue" would be expected to contain about 4 per cent protein and its caloric value can be calculated from the above composition to be about 6200 kcal. per kg. These workers believe the composition of "obesity tissue" is relatively constant from subject to subject and also constant for small and large weight gains. They also express the opinion that the percentage of extracellular water in obesity tissue is approximately the same as in the whole body of reference standard men and that, therefore, the percentage of extracellular fluid, expressed as per cent of body weight, would not be expected to vary with changes in obesity. One component of the extracellular water volume, namely the plasma volume, has been carefully studied by Huff & Feller (110)

in relation to obesity as measured by body density. These investigators found a significant negative correlation between obesity and blood volume expressed as per cent of body weight. Their regression analyses indicated that the amount of blood associated with obesity tissue was about two-thirds that of lean tissue and that women had lower blood volumes per unit weight than men after adjustment for obesity had been made. The inverse relation between blood volume and adiposity has also been reported by Allen *et al.* (111).

In the studies of Passmore *et al.* (112, 113) three constitutionally thin young men were fed diets containing 1300 to 1600 kcal. in excess of daily energy expenditure for 10 to 14 days. These workers confirmed Keys *et al.* 109) in regard to the existence of nitrogen retention during the period of weight gain, finding that approximately 12 per cent of the weight gain was protein. However, in regard to the water content of "obesity tissue," their results were quite different. By two independent methods of calculation they arrived at the conclusion that the weight gain was devoid of water, being composed entirely of fat and nitrogen and that it had a caloric equivalence of 8700 kcal. per kg.

Still another approach was used by Dole and co-workers (114). In five obese women they alternated caloric intake between surplus and deficit every five days to produce cyclical oscillations of body weight. By statistical analysis the changes in body weight specifically correlated with dietary variations could be separated from the general trend and from random changes caused by fluctuations in water balance and errors of measurement. The caloric equivalent of weight loss or gain by this method of computation was found to be from 2200 to 3900 kcal. per kg. This was interpreted as evidence that considerable amounts of water are stored or released as a part of the short term response to caloric imbalance.

It is not possible to reconcile the widely divergent results obtained by these various investigators, but in the present state of knowledge it does not appear to be safe to assume that the composition and caloric value of weight gains and losses are relatively constant.

Studies of skinfold thickness.—That body weight does not always accurately reflect body fatness has been clearly demonstrated [Keys (115), Keys & Brozek (103)]. In recent years several methods have been developed for evaluating obesity more accurately than can be accomplished by body weight measurements. These include measurement of the density of the body, measurement of the total water content of the body, and measurement of the thickness of skinfolds which include the panniculus adiposus (103). The last of these is simple to perform and has been shown to be a relatively reliable index of adiposity [Brozek & Keys (116), Allen *et al.* (117), Pascale *et al.* (118)]. The thickness of the subcutaneous adipose layer can be measured on roentgenograms [Garn (119), Brozek (120)] or, more simply, with calipers specially designed to measure the thickness of a double fold of skin and

subcutaneous tissue Keys (115) Edwards *et al.* (121), Best (122)]. Formulas have been devised for estimation of percentage fat in the body from measurements of skinfolds at selected sites (116, 117, 118). Several recent studies [Newman (123), Garn & Harper (124)] have shown that with increasing adiposity the thickness of the skinfolds on and near the torso increase more than do those on the more distal parts of the extremities. Garn (119) has also shown that the pattern of subcutaneous fat thickness is characteristic of the individual and remains relatively undisturbed when weight is lost. The measurement of skinfold thicknesses is a promising tool in the studies on obesity.

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ENDOCRINOLOGY[1,2]

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The field of endocrine research continues to be a most active one, and the volume of literature is accordingly enormous. Recent reviews have efficiently summarized the work in certain areas. Among these one may cite Harris' volume on neural control of the pituitary (1), Lerner's paper on melanocyte-stimulating hormone (2), the articles of Berson (3) and of Michel (4) on the synthesis and metabolism of thyroid hormone, and Werner's book on physiologic and clinical aspects of thyroid function (5). The adrenal has been extensively reviewed in Hechter & Pincus' discussion of the biogenesis of the adrenocortical secretion (6), in Dorfman & Shipley's volume on androgens (7), in Lieberman & Teich's review of steroid metabolism (8), in the articles of Gaunt *et al.* (9), Dodds *et al.* (10), and Conn (11) on chemical, physiologic, and clinical subjects related to aldosterone, and in von Euler's monograph on the chemistry and pharmacology of norepinephrine (12). The present review, therefore, will confine itself to selected chapters in endocrine research, especially aspects of hypothalamic control of the anterior and posterior pituitary, certain phases of adrenal and thyroid function, and the problems of chromosomal sex.

CENTRAL NERVOUS SYSTEM CONTROL OF THE ANTERIOR PITUITARY

The role of the nervous system in exerting control over anterior pituitary function is a problem which has received wide and intensive study, much of it stimulated by experiments on the reaction of the organism to stressful stimuli, a reaction in part expressed through changes in nervous system (13, 14) and endocrine function (15, 16). There is a large body of evidence indicating that neural structures participate in such reactions, but the precise structures involved, and the exact nature of the anatomic and functional connections between the nervous system and the hypophysis remain controversial matters. It is not the purpose of this review to try to resolve these controversies, which can only be settled by further experimentation, as Munson & Briggs have pointed out (17), but rather to present the principal contributions to the subject and to indicate areas of disagreement.

Anatomic considerations.—Cajal first described nerve fibers passing between the hypothalamus and the pituitary via the pituitary stalk (18).

[1] The survey of literature pertaining to this review was completed in August, 1956.

[2] The following abbreviations are used in this review: ACTH (adrenocorticotropin); ADH (antidiuretic hormone); LH (luteinizing hormone); PBI (protein-bound iodine); TIT (L-3,5,3′-triiodothyronine); TSH (thyroid stimulating hormone).

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Sympathetic fibers associated with the arterial supply to the gland were described by Dandy (19), and Hinsey & Markee (20) suggested that a parasympathetic innervation via the greater superficial petrosal nerve and the carotid plexus might be of importance. The studies of several investigators involving removal of sympathetic and parasympathetic supply to the gland have led to the conclusion that neither system is important in controlling anterior pituitary activity (21, 22, 23). However, Abrams *et al.* (24) have reported impaired estrous response to light in ferrets subjected to bilateral superior cervical ganglionectomy. The paucity of nerve fibers from the hypothalamus which terminate in the pars distalis, described by Rasmussen (25), has led most workers to believe that innervation of this part of the gland is of little significance (26). The question has been re-opened by Vazquez-Lopez & Williams (27) and Metuzals (28) who have found rather numerous fibers terminating in the pars distalis of the rat and horse, respectively, and by reconsideration of the study of Brooks & Gersh (29) which reported a reduction in the number of nerve fibers in all parts of the pituitary after section of the pituitary stalk.

Other structures in the pituitary stalk, viz., the arterial, venous, and portal channels have been extensively studied. Popa & Fielding (30) originally described a hypophyseal portal system and believed that its blood flow was from the pituitary to the median eminence, a view recently espoused by Nowakowski (31). However, the bulk of evidence is that the flow is actually from the median eminence to the gland (32, 33, 34). Details of the blood supply to the human pituitary have recently been presented by McConnell (35) and by Xuereb and co-workers (36, 37).

There is controversy concerning the functional significance of the pituitary stalk. Fortier (38) adopted the view that the stalk serves as "a connecting link between the external environment and the CNS on the one hand, and the pituitary gland and its target organs on the other" (39). The importance of integrity of the stalk, and of the vascular structures in the stalk, in maintaining normal transmission of neural impulses from the hypothalamus to the anterior pituitary has been deduced from three lines of evidence. First, electrical stimulation of the hypothalamus releases LH in the rabbit, producing ovulation, while stimulation of the stalk or of the pituitary itself fails to cause ovulation (40, 41). Stimulation of tuber cinereum and mammillary bodies results in ACTH release while direct stalk or gland stimulation does not (42). Harris (39) felt that these findings supported the idea that stalk stimulation fails to elicit pituitary response because the stalk merely transmits the physiologic stimulus humorally from the hypothalamus.

The second line of evidence deals with stalk section, shown to result in adrenal atrophy (43), and with preparations in which pituitary response after stalk section has been shown to correlate with the degree of vascular regeneration, which can be prevented by imposing a barrier between the cut ends of the stalk (44, 45). Zuckerman and his co-workers (46, 47) have

challenged these observations, and claim that the light-induced estrous response in ferrets can occur even when the hypothalamic-hypophyseal vessels have not regenerated and that the response may fail to be elicited even in the presence of revascularization.

The third line of evidence consists chiefly of the finding that transplantation of the hypophysis to remote sites causes adrenal atrophy, while grafts placed directly beneath the median eminence and revascularized from the hypothalamic-hypophyseal portal system can maintain normal adrenal weight (48). However, the possibility exists that the degree of panhypopituitarism that results from stalk section or transplantation is proportional to the degree of vascular damage suffered by the gland as a result of the manipulation, and is not specifically related to deprivation of the connection between hypophysis and hypothalamus (17, 49, 50, 51). Furthermore, several groups of workers have shown that pituitaries transplanted to the spleen and eye are capable of responding to certain stressful stimuli, whether or not adrenal weight is maintained (52, 53, 54).

Although the concept which would unify these discrepant data is not yet forthcoming, a tentative explanation has been offered by Hume, who suggested that a humoral agent (*v. infra*) might be liberated from a hypothalamic center and transported in the general circulation to the pituitary even in a remote site (55). However, Harris has felt that the dilution of a humoral agent in the systemic blood might render its action too feeble to be effective as a stimulus (1).

The exact groups of cells in the cerebrum which are involved in control of the anterior pituitary are not known with certainty. Green and his coworkers have suggested the possibility that the hippocampus might play a part in hypothalamic activation of the pars distalis (56, 57). Porter (58) found that hippocampal stimulation prevented the eosinopenia caused by epinephrine or surgical trauma. The amygdala has also been implicated by several workers. Abnormal sexual behavior has been produced by bilateral ablation of the amygdaloid regions (59, 60), and although direct proof of the correlation of this finding with pituitary activity is lacking, Green (57) has drawn attention to the numerous connections between amygdala and hypothalamus which would render such a functional connection at least plausible. Further evidence of a connection is provided by the finding that stimulation of the amygdala can cause ovulation in the rabbit [Koikegami *et al.* (61); cited by Green (57)]. Mason (62) has reported significant corticosteroid elevations after stimulation of the amygdaloid nuclei, but not of the putamen or anterior hypothalamus of rhesus monkeys. Green (57) has discussed the possible importance of the "reticular activating system," and Porter (58) has implicated the anterior thalamic nucleus, anterior cingulate gyrus and the orbital surface of the frontal lobe. Gloor (63) has reviewed the evidence suggesting participation by the limbic system. The precise hypothalamic centers involved in control of anterior pituitary secretion are most conveniently treated in terms of the specific anterior pituitary hormones.

Hypothalamic structures.—Long (64) has emphasized the theoretic difficulty of conceiving separate hypothalamic centers for the control of each anterior pituitary hormone. Further, Zuckerman (47) has called attention to the fact that the same changes in hypophyseal function have been reported to follow lesions in different areas of the hypothalamus. For example, Barrnett & Mayer (65) described constant estrus in rats after lesions in the ventromedian nucleus, while Hillarp (66) reported the same dysfunction following lesions below and caudal to the paraventricular nuclei, sparing the ventromedian nuclei. In evaluating the following evidence, it is perhaps well to keep these reservations in mind.

Hypothalamic control of gonadotropin release.—There is considerable evidence supporting the view that the central nervous system may play a part in regulating gonadotropic secretion through its action upon the anterior pituitary, as Marshall (67) pointed out years ago. Many external stimuli have been reported to alter gonadal function, presumably by stimulating gonadotropin release. For example, exposure to light can cause estrus in the ferret (68). There is still disagreement (*v. supra*) as to whether prevention of this estrous reaction can be brought about by pituitary stalk section (44, 69). A number of experimental stimuli have similarly been shown to cause ovulation. Fevold *et al.* (70) demonstrated ovulation in estrous rabbits after intravenous injection of copper acetate, and prevention of this induced ovulation by hypophyseal stalk transection was shown by Brooks and co-workers (71). Nembutal and the barbiturates were shown by Everett & Sawyer (72) to block ovulation in rats, and Barraclough & Sawyer (73) have also succeeded in preventing ovulation with morphine.

Electrical stimulation experiments provided more direct evidence of the role of the hypothalamus in such reactions after Marshall & Verney showed that diffuse stimuli applied to the head caused ovulation in rabbits (74). Harris (41, 75) was able to show that stimulation of the tuber cinereum and posterior hypothalamus resulted in release of LH and ovulation. Similar findings were made by Markee *et al.* (40).

Lesions of the hypothalamus have long been known to cause atrophy of the gonads (76 to 79). Lesions located ventral to the paraventricular nucleus, or in the ventromedian nucleus, have been shown to cause constant estrus, presumably by disturbing the pituitary release of LH (65, 66, 77, 78, 80). Bauer (81) has reviewed the clinical instances of sexual dysfunction in association with hypothalamic lesions, and has reported that the posterior hypothalamus is more likely to be involved in cases of precocious puberty, while the tubero-infundibular and anterior areas tend to be damaged in hypogonadism. This author emphasizes the fact that the sexual disturbances may occur without demonstrable anatomic changes in the pituitary, although the mechanism of production of the disturbance is presumably via that gland.

In animals, the area usually implicated in the production of gonadal atrophy is the tuber cinereum (78). Laqueur *et al.* have demonstrated ovar-

ian abnormalities after destruction of the median eminence and adjacent areas (82). Sawyer & Robison (83) have presented evidence suggesting that the hypothalamic centers controlling ovulation and ovarian weight (tuber cinereum) may be separate from those controlling mating behavior (mammillary bodies in the rabbit, anterior hypothalamic region in the cat). Furthermore, Bogdanove & Halmi (84) and Ganong and co-workers (85) have presented evidence from lesion experiments suggesting that the area of gonadotropic control is separate from that controlling thyrotropin. Finally, Martinez & Bittner (86) have claimed that the cyclic character of estrus is maintained in hypophysectomized female mice with pituitary grafts from either males or females, results which were in accord with earlier work in rats (87). They suggest the possibility that the sex difference in cyclicity may reside in a sex difference of some hypothalamic structure rather than of the pituitary itself (86). The applicability of these data on central nervous system control of gonadotropic function to such clinical problems as "psychogenic amenorrhea" has not yet been established.

Hypothalamic control of thyrotropin secretion.—Clinical interest in the part played by the central nervous system in the control of thyroid function derives largely from the impression that psychic trauma and perhaps a basic personality defect are important factors in precipitating Graves' disease (88, 89), possibly through some unknown hypothalamic-hypophyseal disturbance (90). Experimental attempts to produce emotional and physical stress in animals (rabbits) have been made by Brown-Grant *et al.* who found a decreased rate of thyroidal release of I^{131}, i.e., thyroid, and presumably thyrotropin inhibition, under such conditions (91). Previous studies on the effect of various stressful procedures (epinephrine, typhoid vaccine, trauma, anoxia) had shown decreased I^{131} uptake by rat thyroid (92, 93, 94). Brown-Grant has recently demonstrated increased rates of thyroidal I^{131} release in rats acutely exposed to moderate cold, and decreased rates in animals exposed to severe cold (95). The mechanism of this inhibition is not known with certainty. Since most of the stresses employed cause adrenal cortical activation, and since ACTH or cortisone have been shown to inhibit thyroidal I^{131} uptake (96, 97, 98) and release (99, 100), it has been postulated that the stress-induced reduction in thyroid and thyrotropin function may bear a reciprocal relation to the stress-induced activation of ACTH and of the adrenal cortex (45, 101).

The situation with respect to the adrenal medullary product, epinephrine, is confusing. Epinephrine also produces a decrease in thyroid I^{131} uptake (92, 102, 103). Brown-Grant & Gibson have also shown that both norepinephrine and epinephrine reduce thyroid uptake of radioactive iodine, that this reduction can be caused by surgical trauma and insulin hypoglycemia [conditions known to be associated with epinephrine release (12)], and that the thyroid inhibition by surgical trauma and insulin can usually be abolished by adrenal denervation or demedullation (104). The authors suggest that endogenous epinephrine may inhibit I^{131} uptake during stress.

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The significance of this finding, and the interpretation of it, are rendered less clear by the study of Ackerman & Arons (105) who reported increases in radioactive protein-bound iodine in blood from cannulated thyroid veins of dogs given epinephrine and nor-epinephrine.

Thus, the studies of stressful procedures, thought to act via the central nervous system, corticotropin, and the adrenal cortex or medulla, have not elucidated the essential mechanism of thyrotropin release and thyroid activation.

More direct evidence for a hypothalamic influence on thyroid function has been obtained from experiments utilizing electro-stimulation of the hypothalamus, pituitary stalk section, and hypothalamic lesions. Colfer (106) found histologic signs of increased thyroid activity after electrical stimulation of the hypothalamus, but did not implicate a specific hypothalamic area. Stalk section has, in the hands of most workers, resulted in reduction of thyroid function. Uotila (107, 108) found a failure of the thyroid to undergo hypertrophy in response to a cold environment after division of the stalk. Westman and his co-workers reported histologic evidence of reduced thyroid function after stalk section (109, 110), and Barrnett & Greep (111), in stalk section experiments in which vascular regeneration did not occur, found thyroid atrophy and reduced response to cold and thiouracil. Brown-Grant *et al.* [cited by Harris (39)] performed stalk section in rabbits with precautions to avoid vascular regeneration, and found reduced thyroid uptake and release of I^{131} and prevention of some, but not all of the inhibitory responses of the thyroid to various stresses.

Experiments with electrolytic lesions in the hypothalamus have suggested a separate area which influences thyrotropin secretion. Greer has been able to prevent thiouracil-induced goiter by means of lesions between the suprachiasmatic and caudal ventromedian nuclei (112, 113, 114), in an area more recently thought to be limited to a midline region between the paraventricular nuclei and the median eminence (115). Since iodine-concentrating power of the thyroid remains nearly normal after such lesions, Greer has postulated the existence of two thyrotropins, a "growth" and a "metabolic" factor. He has recently reviewed the evidence in favor of this hypothesis (116). Bogdanove and his co-workers have presented data suggesting that the thyrotropic and gonadotropic mechanisms in rats are under distinct and separate hypothalamic influences, located, respectively, in the anterior hypothalamus and in the area between the median eminence and the pre-mammillary nuclei (84, 117). Ganong and co-workers, working with lesions in dogs, have also gathered evidence indicating separate hypothalamic areas involved in control of gonadotropin, thyrotropin, and adrenocorticotropin release (85, 118). They located the thyrotropin-influencing region in and above the anterior end of the median eminence, and noted that pituitary scarring was slight, and that some intact portal vessels were present in all animals. Further data suggesting separate areas for thyrotropin and corticotropin control were obtained by Greer & Erwin (119), who found that

anterior hypothalamic damage prevented the goitrogenic response to Amphenone (1,2 bis-(*p*-aminophenyl)-2-methyl-propane-1-dihydrochloride) but not the adrenal hypertrophy usually found after administration of this compound (120).

The foregoing evidence, and the finding that radioactive thyroxin is rather selectively concentrated in the median eminence and neurohypophysis (121, 122), have been interpreted to mean that changes in the blood thyroxin level exert their effects upon TSH release by an action on the hypothalamus and not directly on the anterior pituitary (1). In this connection, Euler & Holmgren, working with rabbits, found that injection of thyroxin directly into the anterior pituitary inhibited thyroid I^{131} release but that thyroxin injection into the hypothalamus or median eminence had no such effect (123). From this experiment and from the finding that systemically-administered thyroxin could inhibit thyroidal I^{131} release in animals with ocular grafts of the pituitary (124), the authors concluded that thyroxin exerts its principal effect upon thyrotropin release by a direct pituitary action, a conclusion also reached by Uotila on the basis of stalk section experiments (125).

The role of the hypothalamus and pituitary, i.e., of thyrotropin in the pathogenesis of Graves' disease, remains an unsettled question. Relevant studies which can be appropriately mentioned here are those of Gedda & Lindgren who reported clinical remission in eight cases of Graves' disease after pituitary irradiation by a technic which would also include irradiation of the hypothalamus (126). Noting the refractoriness of the normal pituitary to x-irradiation, Arnold, studying Rhesus monkeys, found degeneration of hypothalamic nuclei after doses of 3000r or more of 23 mev. x-rays (127). He suggested that the beneficial effects of x-irradiation in certain disorders (e.g., Graves' disease, Cushing's syndrome in adrenal hyperplasia) might be mediated through hypothalamic rather than pituitary hypofunction. The validity of this assumption remains to be proved.

Hypothalamic control of adrenocorticotropin release.—This aspect of hypothalamic-hypophyseal relations has called forth the largest body of experimental work in the field, and has been extensively and repeatedly reviewed (1, 13, 17, 39). Again, the methods of approach have consisted chiefly of hypothalamic stimulation, lesions, and pituitary stalk section. Stimulation of the posterior tuber cinereum or mammillary bodies has been reported to cause ACTH release in rabbits, cats, monkeys, and dogs (42, 58, 128, 129). In one human subject, Pool *et al.* were able to cause an increase in plasma corticosteroid level by means of stimulation through electrodes placed near the anterior hypothalamus (130).

The numerous studies on hypothalamic lesions have generally revealed that injury in the floor of the third ventricle, especially in the tuberal or more posterior areas, and in the median eminence, is associated with blockade of corticotropin release following a variety of noxious stimuli (42, 55, 58, 79, 128, 131, 132), but not necessarily associated with adrenal atrophy

(82). Inhibition of adrenal hypertrophy in response to repeated trauma and to amphenone administration has been reported to occur after median eminence lesions (119, 133). Using a more direct assay method for ACTH, viz., measurement of change in adrenal venous 17-OH-corticosteroid level in the hypophysectomized dog (134), Hume & Nelson reported that median eminence lesions blocked ACTH release after operative trauma (135).

Experiments with stalk section have yielded conflicting results. The role of the stalk seemed established by the work of Harris & Jacobsohn who found adrenal cortical atrophy when pituitary transplants were placed in sites remote from the sella (48), but several workers have shown that the transplanted hypophysis can respond to a variety of chemical and stressful stimuli (52, 53, 54). Fortier *et al.* [cited by Harris (39)] have shown that stalk section could cause adrenal atrophy and could prevent the normal ACTH release in response to some but not all stresses. Such evidence as this may modify Fortier's "dual" control theory of ACTH regulation (136). Renewed interest in the role of the hypothalamic-pituitary vascular connection has followed the studies of Porter and his co-workers, who detected a substance from the hypophyseal portal vein blood of dogs which was apparently capable of releasing corticotropin from the anterior pituitary (137, 138).

One of the reasons for certain discrepancies in the experimental data cited above may well be that different indices of adrenal cortical activity were employed by different investigators. Some of these indices carry a higher degree of specificity than others. For example, the conclusions drawn from experiments utilizing changes in circulating lymphocytes and eosinophiles should perhaps be viewed with more reservation than those in which depletion of adrenal ascorbic acid or rises in plasma 17-OH-corticosteroid levels were measured.

The nature of the chemical transmission of impulses from the hypothalamus causing ACTH release.—The morphologic studies of Wislocki & King (32) had shown that the hypophyseal portal blood vessels had only an indirect connection with the pars distalis. It became necessary to postulate the transmission of hypothalamic impulses to the anterior pituitary via the portal system by means of some humoral mechanism (1, 39, 45). The theories implicating the role of the blood level of adrenal cortical secretion in controlling ACTH release are well known and have been reviewed adequately (1, 16). Similarly, the part played by adrenal medullary secretion of epinephrine in response to stress has been extensively reviewed by Harris (1) and by Munson & Briggs (17). The latter authors summarize the work from their own and other laboratories, and conclude, partly because of their finding that epinephrine cannot stimulate the pituitary fast enough to mediate many rapidly-acting stimuli, that epinephrine probably is not the chemotransmitter. It is interesting that although epinephrine produces adrenal activation (139) and elevated blood ACTH (140) in animals, it causes no rise in plasma 17-hydroxycorticosteroid levels in man (141).

Vasopressin has also been suggested as a chemotransmitter for ACTH release by Mirsky (142, 143) and others. Many workers have shown that crude or purified vasopressin can produce corticotropin release, as measured by a variety of assay technics (131, 143 to 154). Although oxytocin has been shown to be inactive in depleting adrenal ascorbic acid (143) Martini and his co-workers have claimed that oxytocic hormone can also bring about ACTH release (152, 153). Since vasopressin, and in some situations oxytocin, are reportedly liberated during stress (143), since there is increasing evidence that the posterior pituitary hormones may be synthesized in the hypothalamus (155), and since the so-called "neuro-secretory" granules in the hypothalamus have been reported to be decreased after stress (156), Mirksy and others have felt that vasopressin may well be the chemical transmitter which reaches the pars distalis via the hypophyseal portal vessels and is responsible for corticotropin release during stress (143).

Evidence against this view has been presented by Briggs & Munson who were able to block ACTH release by vasopressin with morphine (157), by Swingle *et al.* who found that the ACTH-releasing substance in commercial Pitressin (150) was probably identical with the releasing material in "substance P" obtained from an extra-hypothalamic site (158), and by the *in vitro* studies of Guillemin & Rosenberg who found that the extract of posterior hypothalamus or median eminence which caused pituitary ACTH production in tissue culture contained no Pitressin (159), and that pure arginine-vasopressin did not cause ACTH release from the *in vitro* pituitary (160, 161).

Other substances have been implicated as "neurohumoral" agents. A frequently employed experimental approach has been the administration of a material after prior administration of a drug known to block the action of the first. As Harris has summarized the results of these studies, administration of adrenolytic and anti-cholinergic agents has not brought forth convincing evidence that adrenergic or cholinergic influences are indispensable in producing ACTH-release (1). This point of view was reinforced by Guillemin who found that while dibenzyline and atropine could block the ACTH-release caused by epinephrine and acetyl-beta-methylcholine respectively, neither lytic agent could prevent the ACTH-release following nonspecific stress (160). The suppressive effect of the nervous system depressant morphine on ACTH-release following many stresses (histamine, epinephrine, vasopressin, laparotomy, unilateral adrenalectomy in morphine-adapted animals) has been alluded to above (17, 157), though other workers had shown that morphine itself could produce adrenal activation and presumably release of ACTH (162, 163, 164). Similarly, the broadly acting agent 10-(gamma-dimethylaminopropyl)-2-chlorophenothiazine (chlorpromazine, largactil) has been reported to cause corticotropin release (165 to 168), and also to block the ACTH-release following the stresses of operative shock and insulin hypoglycemia (167, 169 to 172), although the block could not invariably be demonstrated (173, 174). Equivocal effects of the drug on

gonadotropin release have also been described (175). The blockade of corticotropin secretion produced by morphine and chlorpromazine does not elucidate the nature of the chemotransmitter, but since both drugs are central nervous system depressants, and since both, especially chlorpromazine (176, 177), may act on the hypothalamus in particular, the findings re-emphasize the importance of some neural element in the control of corticotropin. This view is perhaps supported by the study of Century & Horwitt who found that chlorpromazine depressed oxidative phosphorylation by rat brain homogenates (178).

Some of the most provocative evidence bearing on the importance of neural tissue in influencing ACTH release has been provided by the study of Slusher & Roberts who showed stimulation of ACTH secretion *in vivo* after administration of an extract of bovine posterior hypothalamus which was effective even in rats with hypothalamic lesions which prevented adrenal response to other agents (179). Equally provocative evidence has been presented by Guillemin and his co-workers who have shown *in vitro* ACTH production by posterior (but not anterior) hypothalamic tissue (159), the essential factor in which is probably not epinephrine, histamine, serotonin, vasopressin, or oxytocin (159, 180). Schapiro *et al.* have also found a pituitary-stimulating substance in the brain blood of hypophysectomized rats after electric shock stress (181). A similarly acting substance from hypophyseal portal blood of dogs has been mentioned above (137, 138).

Hypothalamic control of other hormones.—Harris has reviewed the evidence for and against hypothalamic control of lactogenic and growth hormones (1). Rauschkolb & Farrell have suggested that there may be a direct hypothalamic control of aldosterone secretion (182), and Pool *et al.* have obtained some evidence in man for a possible direct central nervous system influence over corticosteroid secretion (130). Evidence has been presented suggesting separate hypothalamic areas capable of causing release of epinephrine and nor-epinephrine, respectively (183, 184).

Summary.—It seems obvious that the hypothalamus plays an important role in the regulation of the release of gonadotropic, thyrotropic, and adrenocorticotropic hormones. There is suggestive evidence that the hypothalamic areas controlling these different mechanisms may be separate. The precise role of the pituitary stalk and of the hypophyseal portal blood vessels in transmitting the hypothalamic control is not finally settled. The nature of the hypothalamic "humor" which presumably transmits neural stimuli to the pars distalis remains unknown, but there are data which suggest that it is not epinephrine, vasopressin, or histamine.

The Posterior Pituitary

The role of the supraoptico-hypophyseal tract in the regulation of release of ADH seemed well established by the work of Fisher *et al.* (185). Recent studies, summarized by Scharrer & Scharrer (155) and by Hild (186), have

raised the strong possibility that the site of formation of posterior pituitary hormones is the hypothalamus, and not the neural lobe. The theory of a "neurosecretory" origin of these hormones could explain the lack of glandular cells in the neurohypophysis, and the presence of antidiuretic material in the hypothalamus (187, 188). It could also explain the decrease of ADH and stainable "neurosecretory" substance in the neural lobe, and the increase of both in the hypothalamus after section of the pituitary stalk (189). Dehydration has long been known to result in depletion of neurohypophyseal ADH (190 to 193). Similarly, Leveque & Scharrer have shown that hypothalamic ADH and neurosecretory (Gomori-stainable) material are depleted by dehydration, and restored after water is again supplied (194). The finding of ADH (195) and oxytocin (196, 197) in the diencephalon after removal of the posterior pituitary or hypophysectomy, lends further credibility to the idea of a supra-hypophyseal origin of these hormones. However, Harris, in a thorough review of this subject (1), points out that the neurosecretory thesis should not necessarily negate entirely the classic view of Ranson and his colleagues (185). The role of blood osmotic pressure in regulation of ADH secretion (198, 199), the clinical application of this principle to the clinical diagnosis of diabetes insipidus (200, 201), and the part played by epinephrine in preventing ADH release during emotional stress (202) are too well known to require extensive review.

Other factors involved in regulation of posterior pituitary hormones have been recently studied. For example, emotional stress in animals has been shown to result in failure of oxytocin release from the posterior pituitary (203), a failure which may in part be related to activation of sympathetic centers (204). Concerning the part played by adrenocortical steroids in influencing ADH release, Gaunt *et al.* have presented evidence indicating that glucocorticoids may prevent the depletion of neurosecretory substance occurring in adrenalectomized animals during dehydration (205), and Dingman & Despointes have claimed that such steroids may inhibit ADH-controlling impulses from the hypothalamus in man (206).

Further studies of physiologic actions of posterior pituitary hormones have demonstrated that the water re-absorption caused by vasopressin is (approximately) a function of the square root of the rate of vasopressin infusion (207). Friedman *et al.* have shown that dosage may determine the degree of excretion versus retention of sodium by the kidney (208). Ingle has reported that vasopressin appears to be the substance (contaminant) in ACTH which is essential as a supplement to adrenal cortical extract in maintenance of normal muscle work in the hypophysectomized animal (209). Wagner & Braunwald have observed a blood pressure-maintaining effect of vasopressin in orthostatic hypotension (210), and Berliner & Davidson, in an ingenious experiment, have shown that ADH is not an essential for the formation of a hypertonic urine (211). Leaf & Renshaw (212) have extended the fundamental studies of Ussing (213) concerning the effects of ADH on cell membrane permeability, and have confirmed the fact that the

hormone increases sodium transport with respect to oxygen consumption.

So far as the metabolism of ADH in the body is concerned, it has been known that liver tissue can inactivate this hormone (214). Zaidi has been able to show that ADH is also inactivated by kidney tissue *in vitro* and *in vivo* (215). Oxytocin has been shown to be inactivated by placental extracts and by pregnancy plasma (216).

A number of studies have been carried out in which estimates of "antidiuretic substances" have been made by a variety of technics. In view of the reservations voiced by van Dyke and co-workers (217) concerning the specificity of some of these assays, the interpretation of results should perhaps be accepted with certain reservations. Ralli and co-workers (218, 219) and Eisenmenger *et al.* (220, 221) have raised the question of increased ADH activity as one of the causal mechanisms in ascites formation in hepatic cirrhosis. This idea has recently been called into question from several different directions. There is no evidence that patients with liver disease fail to inactivate ADH (222, 223). Lamdin *et al.* were unable to find amelioration of impaired water diuresis in cirrhotic patients given ethanol (224), a substance known to inhibit ADH secretion (225 to 227), and Goldman & Luchsinger could not detect excessive antidiuretic substance in the urine of patients with cirrhosis (228). Although Murdaugh (229) claimed diuresis after ethanol in certain hyponatremic states thought to be associated with excessive anti-diuretic activity (postoperative oliguria, refractory congestive heart failure), at least two groups of investigators have been unable to correlate quantities of blood or urinary anti-diuretic activity either with diurnal variation of urine flow (230) or with the existence of congestive failure (228). Laragh *et al.* have shown that experimental ascites (inferior vena cava constriction) could occur in dogs with diabetes insipidus having little or no demonstrable ADH in the neurohypophysis at autopsy (231).

Additional clinical studies have revealed a relative resistance of hyperthyroid patients to the anti-diuretic effects of vasopressin (232), an interesting observation in view of the ameliorative effect of thyroidectomy, and the enhancing action of thyroid hormone upon the polyuria of diabetes insipidus (233 to 238). Lipsett *et al.* have attempted to characterize the polyuria following hypophysectomy in man, and have found that the presence or absence of polyuria did not necessarily indicate the completeness of hypophysectomy, and that response to hypertonic saline did not always distinguish between psychogenic and organically determined polyuria (239). They emphasize the importance of the amount of functioning tissue in the supraoptic-pars nervosa system in determining degree of polyuria. Doxiades & Tiliakos have emphasized the rarity of diabetes insipidus in post-partum necrosis of the pituitary, and report a single patient in whom the syndrome started four weeks after delivery and lasted for three years (240).

Probably the most significant advances in this area have been made by du Vigneaud and his co-workers, who have reported the synthesis of a polypeptide which has all the physiologic features of oxytocin (241), and have

made important progress toward the synthesis of arginine vasopressin (242). The possible significance of these substances in the transmission of hypothalamic-anterior hypophyseal impulses has been discussed above (cf. section on central nervous system control of the anterior pituitary).

The Thyroid

Synthesis of thyroid hormone.—After the isolation of thyroxine from the thyroid (243), its identification (244) and synthesis by the coupling of two molecules of diiodotyrosine (245), and the identification of diiodotyrosine in thyroid tissue (246), most workers believed that the biosynthesis of thyroxine is accomplished by coupling of two diiodotyrosines with loss of one alanine side chain. It is not known whether or not this reaction requires enzymatic catalysis (247). Because peptide-linked acetylated diiodotyrosine derivatives yielded larger quantities of the corresponding thyroxine derivatives, it has been thought that the coupling reaction occurs within the thyroglobulin molecule, rather than with the amino acids in the free state (248).

Additional iodinated amino acids, monoiodotyrosine (249), L-3,5,3′-triiodothyronine (TIT) (250 to 255), L-3,3′-diiodothyronine, and L-3,3′,5′-triiodothyronine (256) have been isolated from the thyroid. The mechanism of biosynthesis of TIT, physiologically the most active of these, remains unknown. Roche & Michel (257) and Michel (4) have analyzed two possible mechanisms, deiodination of thyroxine, and condensation of monoiodotyrosine with diiodotyrosine. They consider that the evidence favoring one pathway to the exclusion of the other is not compelling.

Certain clinical disorders may be characterized by derangements in biosynthesis of thyroid hormone. Stanbury *et al.* (258) have reported the appearance of mono- and diiodotyrosine in the blood of a goitrous adult with hypothyroidism after I^{131} administration, although these compounds are generally not found in the serum of normal subjects (259 to 262), and are found only inconstantly in hyperthyroid patients (263, 264). Stanbury *et al.* postulated that the biosynthetic defect consisted of an excessive formation and release of mono- and diiodotyrosine, hormone precursors, with synthesis of minute quantities of thyroxine (258), a defect different from those previously described in goitrous cretins (265, 266, 267). In functional thyroid carcinoma, Robbins & Rall and co-workers have described a serum iodine compound different from the products of normal thyroid metabolism (268, 269). The precise nature of this iodinated substance and its significance remain to be elucidated.

Nature of "tissue" and circulating forms of thyroid hormone.—With the finding that TIT possessed greater antigoitrogenic and calorigenic effects than thyroxine in animals and man, the question of the identity of the "true" thyroid principle, hitherto believed to be thyroxine (247, 259), was reopened. Since TIT acted more rapidly *in vitro* (270) and *in vivo* (253, 271 to 278), was known to appear in plasma after I^{131} and thyroxine administration, and to be a constituent of normal and hyperthyroid plasma (250, 279,

280), since thyroxine could be shown to be de-iodinated to TIT in extrathyroidal sites (281) with the latter perhaps penetrating more readily into cells (282), it seemed reasonable to postulate TIT as the tissue form of thyroid hormone. However, Gross *et al.* suggested that this might not be the case, in view of the still appreciable latent period between TIT administration and its physiologic effect (283). Furthermore, although thyroxine and TIT both "uncouple" oxidation from phosphorylation in mitochondrial preparations (284), the over-all augmentation of oxygen consumption is rather small (285), and neither hormone increases the Q_{O_2} of tissue slices, i.e., of intact cells (270, 286, 287). Roche & Michel *et al.* (288 to 290) have reported the identification in kidney tissue of labeled triiodothyroacetic acid after administration of radioactive TIT. In an analogous experiment Albright and co-workers have described the formation of labeled tetra-iodothyroacetic acid after administration of thyroxine-I^{131} (291). In view of the finding of Thibault & Pitt-Rivers (292) that *in vitro* addition of either "triac" or "tetrac" to rat kidney slices (i.e., intact cells) caused immediate acceleration of oxygen uptake, it was postulated that these acetic acid analogues might indeed be the long-sought tissue forms. Clinical and experimental data on this point have been reviewed in detail by Dodds *et al.* (10). Wiswell & Asper (293) have recently reported that "triac" and "tetrac" actually showed less metabolic activity *in vitro* and *in vivo* (in man) than triiodothyronine and thyroxine. Thus Berson, in a critical review of pathways of iodine metabolism, has raised the proper question of whether an acetic acid analogue is the "tissue" form of thyroid hormone or merely another metabolic product, and has concluded that this remains for the moment a matter of speculation (3). The problem is further complicated by such findings as those of Tomita & Lardy (294) who reported that a synthetic product, "thyronamine" (3,5-diiodo-4-(3′-iodo-4′hydroxy-phenoxy)phenethylamine), is 36 times more potent than L-thyroxine in several different assays.

The identity of the circulating form of thyroid hormone appears to be a less controversial matter. There is general agreement that most of the protein-bound iodine in serum is in the form of thyroxine in normal individuals (259, 295) and in patients with Graves' disease (296), and that most of the binding of thyroxine at physiologic serum concentrations occurs in the "interalpha" region between $alpha_1$- and $alpha_2$-globulin (297, 298, 299). Most of the "thyroxine-binding protein" appears to be in Cohn fractions IV-6 and IV-9 (300). Triiodothyronine is also bound to the alpha-globulin fraction (299, 301), but more loosely than thyroxine, which can displace TIT from its binding site (299). Administered TIT disappears from plasma more rapidly than thyroxine (274, 282, 299, 302, 303) possibly because of its weaker affinity for serum protein (303, 304). Robbins & Rall have pointed out certain discordances in the correlation between protein-binding characteristics of various thyroxine analogues and their metabolic activity (305).

Studies of thyroxine-binding capacity in pathologic states have been carried out. Recant reported abnormal thyroxine-binding (to alpha$_2$-globulin) *in vitro* with high concentrations of thyroxine-I^{131} in the serum of nephrotic subjects, an abnormality apparently not dependent upon hypoalbuminemia (306). On the other hand, in an *in vivo* study, Rasmussen found a normal pattern of PBI^{131}-binding in the serum of nephrotic patients (307). Hamolsky has postulated qualitative abnormalities in the relationships among serum protein, thyroid hormone, and tissue factors in thyroid disorders, following the observation that rat diaphragm and human red cells showed a greater "uptake" of labeled TIT and thyroxine from hyperthyroid than from euthyroid plasma (308). Sterling & Chodos have pointed out the possible role of abnormalities in thyroxine-binding protein in accounting for the more rapid rate of extrathryoidal hormone turnover and degradation which they found in thyrotoxicosis and in hypermetabolism without thyroid disease (309).

Adrenal-thyroid relationships.—Despite a large number of studies of the effects of changes in thyroid activity upon adrenal function and of adrenocortical influence over thyroid function, the inter-relationships between the two glands are not clearly understood, nor is there general agreement concerning the clinical significance of such relationships. Thyroidectomized or thiouracil-treated animals have usually been reported to develop adrenal atrophy (310 to 313), and in a recent autopsy study Berkheiser reported diminution in adrenocortical width in a case of human myxedema (314). On the other hand, Russfield (315) has described adrenal enlargement and nodularity in hypothyroidism. Urinary 17-ketosteroid values are often low in myxedema (316 to 320) and may (320) or may not (321) return to normal when thyroid is given. Urinary corticosteroid levels have also been reported to be reduced in hypothyroidism (101, 322). Plasma 17-OH-corticosteroid levels in human myxedema have been described as normal, possibly because of a slower rate of cortisol disappearance from plasma, an abnormality which has been detected by Levin & Daughaday (101) and by Peterson *et al.* (323). Response of the adrenal cortex to ACTH in clinical and experimental thyroid deficiency has been said to be normal (324, 325, 326) or reduced (327). Asper & Wiswell (328) have emphasized the occasional difficulty of distinguishing clinically between the adrenal insufficiency (or what may simulate adrenal insufficiency) associated with primary myxedema, and that associated with intrinsic adrenal disease or with pituitary deficiency. The problem of differential diagnosis of primary versus secondary myxedema has been fully discussed by Van Arsdel & Williams (329).

In hyperthyroidism the adrenals have variously been described as small (330), large (315), and normal (331), though thyroid feeding usually causes adrenal enlargement in animals (332, 333). Urinary steroid excretion may be normal or subnormal (316 to 320) in clinical thyrotoxicosis. Russfield (315) has reported adrenal hyperplasia in five of ten hyperthyroid patients, though urinary 17-ketosteroid values were normal. In a small number of

thyrotoxic subjects Perkoff *et al.* (334) and Wallace *et al.* (335) found normal plasma 17-OH-corticosteroid levels. This finding must be viewed in the light of the report of Peterson and co-workers to the effect that administered cortisol usually disappears from plasma at an accelerated rate in hyperthyroidism (323). Under experimental conditions thyroxine feeding has been said to increase urinary (101) and, in thyroidectomized animals, plasma (327) 17-OH-corticosteroids.

With respect to adrenal effects upon thyroid function, the possible reciprocity between ACTH and TSH release (45) and possible adrenal medullary effects on the thyroid are discussed in the section on hypothalamic control of thyrotropin secretion (*v. supra*). In the rat Uotila & Kannas reported reduced epithelium and increased colloid in the thyroid after cortisone treatment (336). In man and animals adrenal steroids have been shown to reduce thyroidal I^{131} uptake (337, 338) and release (45), effects which Paris *et al.*, (339) have shown may not be ascribable to an increase in renal I^{131} clearance, the mechanism of which has been studied by Bricker & Hlad (340). Ingbar & Freinkel (341), taking cognizance of the low circulating thyroid hormone levels following cortisone administration (337, 338, 342, 343, 344), were unable to show any abnormality in the rate of peripheral degradation of administered thyroxine in patients treated with adrenal steroids or ACTH, or in a subject with endogenous hyperadrenocorticism. These authors thus state the present position with regard to the effects of adrenal cortical steroids upon thyroid activity: "Whether the decline in SPI [serum precipitable iodine] results from a diminution in the glandular production of hormone, the rate of turnover of the glandular hormone pool, or both, and whether it is mediated by an action of cortisone on the pituitary gland or directly on the thyroid remains to be elucidated" (341).

Clinical studies.—Advances in technics of diagnosis of clinical disorders of the thyroid have been made by several groups of investigators. Blackburn & Power (345) have concluded that determination of the serum protein-bound iodine level by the method of Barker (346) was the most valuable single test in clinical evaluation of thyroid function. Hughes & Miller have devised modifications using PBI^{131} (347), and Goldsmith & Eisele have shown deceleration of PBI^{131} release in hyperthyroidism after sodium iodide administration (348). Hare & Haigh (349) have pointed out the very considerable day-to-day variations which may occur in normal subjects in the thyroidal uptake of I^{131}. Lamberg *et al.* have confirmed the usefulness of intramuscular injection of TSH and measurement of serum PBI in the differential diagnosis of primary and secondary myxedema, and have indicated that intravenous administration of TSH with measurement of PBI offers no diagnostic advantage (350). Martin & Stanbury have indicated the variability of TSH effect upon thyroidal I^{131} uptake in the I^{131}-treated gland (351). Gilliland & Strudwick (352) have applied their TSH assay (353) to clinical cases of thyrotoxicosis with and without severe exophthal-

mos, and have reaffirmed their view that excess levels of "orthodox" TSH cannot be incriminated as the cause of hyperophthalmic Graves' disease. The larger question of the origin of Graves' disease has been reviewed by Dobyns (354), and the evidence for (355) and against (356) TSH as an important factor in the pathogenesis of diffuse toxic goiter has been summarized by Rawson and Werner, respectively. A pertinent report by Albeaux-Fernet *et al.* described remission in Graves' disease following hypophysectomy (357). Various refinements in the use of I^{131} as a diagnostic tool have been presented by Oddie *et al.* (358), Rall (359), and McConahey and co-workers (360).

In studies of clinical myxedema Pathy has reported a case of multiple serous effusions in association with hypothyroidism (361), and Fraser & Garrod have collected four cases of what appeared to be primary myxedema without gonadal or adrenal insufficiency dating from post-partum shock (362). Goldstone & Ford reported two cases of severe myotonia in association with myxedema which cleared on thyroid replacement therapy (363), while Jacobson *et al.* have presented eight cases of dystrophia myotonica who exhibited low basal metabolic rates but normal PBI and I^{131} uptake (364). Crispell *et al.* have shown that TIT increased the rate of incorporation of N^{15} glycine into protein in myxedematous subjects, and emphasized that this technic may afford insight not obtainable by classical nitrogen balance studies (365). Jones *et al.* demonstrated an increase in plasma lipide components in myxedema which was qualitatively similar to that seen in atherosclerotic patients, though the latter group showed greater elevations in the beta-lipoprotein fraction (366). Best and co-workers reported that beta-sitosterol had a similar quantitative effect in lowering serum cholesterol levels in myxedematous patients and in normal subjects (367).

The question of the pathogenesis of Graves' disease has been referred to above, and must be left open for the present. A pertinent study, which raises the possibility of a constitutional abnormality in this disease, was made by Ingbar *et al.* who demonstrated changes in thyroxine turnover and increases in thyroidal I^{131} uptake in euthyroid relatives of patients with Graves' disease (368).

Engstrom & Markhardt (369), studying the response of circulating thyroid hormone to stress in man (*v. supra*), found no acute changes in serum precipitable iodine levels. The significance of this observation is not clear at this time.

The Adrenal Medulla

The pressor effect of certain aqueous extracts of adrenal tissue was demonstrated as long ago as 1895 by Oliver & Schäfer (370), and in 1897 Abel & Crawford identified epinephrine as one of the active principles in adrenal medullary tissue (371). Cannon & Rosenblueth (372) reasoned that epinephrine was not the only substance which accounted for the effects of sympathetic nerve stimulation, and postulated the existence of another

substance which they called "Sympathin E." The experiments of Bacq (373) suggested the similarity between the actions of "Sympathin E" and nor-epinephrine. Bacq's view was supported by the work of several investigators (374 to 376), and Euler (377, 378), using pharmacologic methods, was able to detect nor-epinephrine in extracts from several structures, including adrenergic nerves. The presence of this amine was then demonstrated in bovine adrenal glands (379, 380, 381) and in the human adrenal (379, 382), in which it is thought to contribute about 20 to 25 per cent of the total amine output of the normal adult medulla, and approximately 90 per cent of total pressor amine production by the adrenal medulla of children (382, 383).

The steps involved in the biosynthesis of epinephrine and nor-epinephrine remain in large part unknown. Euler (12) has reviewed the evidence bearing on this difficult chemical point. Blaschko (384, 385) theorized that L-dopa-decarboxylase might play a role in the formation of adrenaline from L-tyrosine in a series of reactions in which nor-epinephrine acts as an intermediate or precursor. As a result of studies with C^{14}-labeled phenylalanine Gurin & Delluva (386) suggested that this amino acid could be a nor-epinephrine precursor. Since methylation of nor-epinephrine to epinephrine can occur *in vitro*, it has been postulated that nor-epinephrine may be a normal precursor of epinephrine (387).

The localization of the sympathetic amines in submicroscopic granules of adrenal medullary cells affords a further means of chemical study relating to biosynthesis (388, 389, 390). For example, these storage granules have been shown to contain a large proportion of the cytoplasmic protein, an appreciable portion of phospholipide (391), high concentrations of organic phosphates (392), cytochrome oxidase, succinoxidase, and amine oxidase activity (393), most of the cellular acid phosphatase activity, and an adenosinetriphosphate-dephosphorylating system (394). These granules may (393) or may not (394) be related to true mitochondria. After ultracentrifugation the dopa-decarboxylase activity alluded to above was found in the supernatant of adrenal medullary preparations and not in the granular fraction (393). Nor-epinephrine can be released from the granules of chromaffin cells (390) and from adrenergic nerves (395) by membrane active substances (digitonin, detergents, and increased potassium ion concentration), suggesting that the amine is stored in structures limited by a membrane which at rest is impermeable to the amine.

Metabolism of endogenous and injected sympathomimetic amines has been extensively studied. That ingested epinephrine is excreted by way of the kidneys was first shown by Richter (396), and catecholamines were later detected in normal human urine by Holtz *et al.* (397) and Euler & Hellner (398). Urinary excretion would appear to be a relatively unimportant factor in the disposal of these amines (399), accounting for no more than 6 per cent of administered nor-epinephrine (400) and epinephrine (401, 402) in free and conjugated forms. Monoamine oxidase appears to

be an important enzyme in the degradation of these substances, being responsible for metabolism of about 50 per cent of administered epinephrine (403) and a major portion of administered nor-epinephrine (404). This degradation can be inhibited by amine oxidase inhibitors such as iproniazid (404). The possible importance of other enzymes, e.g. peroxidases (402), cytochrome oxidases, and epinephrine dehydrogenase has been reviewed by Euler (12).

The actual amount of free nor-epinephrine in human urine probably varies from 25 to 50 μg. per 24 hr., while epinephrine is present in amounts of 4 to 8 μg. per day (12), a ratio which is the reverse of that obtaining in adrenal medullary tissue. The urinary nor-epinephrine content of normal individuals is essentially unchanged by adrenalectomy and is present in normal quantity in Addison's disease (405, 406), while epinephrine values fall almost to zero (407). On the other hand, urinary excretion of nor-epinephrine is subnormal after thoracolumbar sympathectomy (408). Quantitation of catecholamines in plasma reveals the presence of minute amounts: epinephrine 0.5 μg. per liter (SD 0.7), and nor-epinephrine 3.5 μg. per liter (SD 1.1) (409, 410). Such chemical methods are based upon the fluorescence of the oxidation products adrenolutine and nor-adrenolutine. Details of the fluorimetric technics have been described by Lund (411 to 414), Balsiger *et al.* (415) and Goldenberg *et al.* (416), and paper chromatographic separation has been devised by James & Kilbey (417). A critical evaluation of bioassay and fluorimetric methods has been exhaustively presented by Goldenberg *et al.* (416).

The pharmacologic properties of epinephrine and nor-epinephrine are well enough known not to require extensive review. The subject has been discussed in detail by Euler (12) and by Jailer & Longson (418). It suffices to remind the reader of the profound differences between the effects of the two amines, especially in terms of the cardiovascular system, as shown by Starr *et al.* (419), Ranges & Bradley (420), McMichael & Sharpey-Schafer (421) and Goldenberg *et al.* (422), who have emphasized the fourfold potency of nor-epinephrine over epinephrine as a peripheral vasoconstrictor and the relative lack of effect of the former on cardiac output. The fall in peripheral resistance which occurs with epinephrine, and its prevention of the vasoconstricting action of nor-epinephrine when the two are simultaneously administered, have been thought to be on the basis of competitive inhibition (423).

Bioassay and chemical methods have been utilized in attempts to clarify some of the factors involved in control of adrenal medullary secretion. Increased amine production by the medulla has been shown to occur via the carotid sinus reflex (424), after afferent nerve stimulation (425), after hypothalamic stimulation (183), after asphyxia (425), with insulin hypoglycemia (426, 427, 428) [although Weil-Malherbe & Bone (429) described a fall in blood epinephrine under these conditions], during strenuous muscular work and hemorrhagic hypotension (430), during exposure to cold (431), and fol-

lowing splanchnic nerve stimulation (432). Dunér (433) showed a fall in medullary secretion associated with hyperglycemia, and decreased catecholamines in plasma have been said to occur in pentobarbital anesthesia (434). Epinephrine, but not nor-epinephrine, has been said to be lower during natural sleep in man (435). Other conditions which have been shown to cause increased output of catecholamines in human subjects include myocardial infarction (436), administration of ACTH or cortisone (437), complications of surgery (438), emotional stress (439, 440), and electroconvulsive therapy (441, 442).

The chief clinical interest in measurement of catecholamines has centered around the findings in pheochromocytoma. Increased values were shown in patients with these tumors by Engel & Euler (443), Goldenberg & Rapport (406), and Euler (444). In the cases reported by Lund (414) 24-hour excretion amounted to more than 2500 μg. of nor-epinephrine and 700 μg. of epinephrine. Contrary to the data of Holtz *et al.* (397), patients with essential hypertension rarely, if ever, excrete elevated catecholamine levels in the urine when tested by modern methods (405, 416, 445). The diagnostic use of adrenolytic agents such as N:N-dibenzyl-beta-chloroethylamine (Dibenamine) (446), Benzodioxane (447, 448, 449), and Regitine (2(N-*p*-tolyl-N(m-hydroxyphenyl)-aminoethyl)-imidazoline hydrochloride) (447, 450) utilizes the ability of these substances to oppose the hypertensive effects of circulating pressor amines. In patients with pheochromocytoma studied during a normotensive phase of their disease, agents which provoke attacks of hypertension (presumably attributable to stimulation of epinephrine or nor-epinephrine release from the tumor, though this mechanism is unproved (12)) have been used. Such drugs include histamine (451, 452), tetra-ethyl ammonium chloride (453), and acetyl-beta-methylcholine (454). Goldenberg *et al.* (416) have demonstrated the greater specificity of estimation of catecholamines in urine, a technic which usually obviates the false negative and false positive results frequently yielded by the above pharmacologic testing procedures. Estimation of catecholamines in urine is performed after adsorption on aluminum hydroxide, followed by elution, paper chromatography and absolute quantitation of epinephrine and nor-epinephrine by photofluorimetry (416). In their hands, no false negative or positive results were observed in 16 cases of pheochromocytoma and 91 cases of essential hypertension with this rather elaborate chemical procedure.

As is the case with other hormones, there has been more interest in recent years in the study of the more basic mechanisms of action of sympathomimetic amines. For example, King & Baldwin have demonstrated proteinuria to be associated with reductions in renal plasma flow, glomerular filtration rate, and urine flow during infusion of epinephrine and nor-epinephrine in man (455), which was not the case with the smaller doses previously given by Smythe *et al.* (456). The latter substance produced no change in tubular transfer maximum for glucose. DiSalvo *et al.* (457) were

able to block the metabolic and circulatory changes caused by insulin hypoglycemia (but not by infused epinephrine) with hexamethonium or tetra-ethyl ammonium chloride. (These authors point out that the increased blood levels of lactic acid associated with epinephrine, but not with nor-epinephrine, might be of use in detecting pheochromocytomas which secrete predominantly epinephrine.) It is noteworthy that in a case of secreting pheochromocytoma studied at the Barnes Hospital in St. Louis, there was some fall in blood pressure after administration of hydralazine plus hexamethonium (458).

Influences of these amines upon chemical processes have also been studied. Dury & DiLuzio have found that epinephrine can cause moderate changes in plasma lipide inter-relationships, and an increased rate of P^{32} incorporation into the aorta of rabbits (459). In inquiries into the actions of these substances on carbohydrate metabolism in rats, Bloom & Russell have confirmed the observation that nor-epinephrine has much less effect than epinephrine in raising blood glucose and lactate levels, though increases in myocardial glycogen occurred with both amines (460). The activity of liver phosphorylase (461) is enhanced, and the incorporation of P^{32} into phosphorylase greatly accelerated (462) by epinephrine. Studies of nor-epinephrine action on the metabolism of ions have revealed that acute administration of the amine can cause decreases in arterial wall potassium concentration and occasionally increases in sodium (463), and presumably, increases in apparent potassium turnover rate in myocardial cells (464). A functional interpretation of these findings is not readily forthcoming, but the data, of course, raise interesting questions concerning the effects of epinephrine and nor-epinephrine upon the permeability of cell membranes.

The Adrenal Cortex

The metabolism of adrenocortical steroids.—The study of the absorption, distribution, and excretion of adrenal cortical hormones has been greatly simplified by methodologic advances which have proved to be applicable to clinical problems. The general problem of the catabolic fate of steroid hormones has been summarized by Lieberman & Teich (8) from a chemical point of view, so that the present review will concern itself with topics of clinical applicability. Since the demonstration by Romanoff *et al.* (465), and by Bush & Sandberg (466), that cortisol (hydrocortisone, "compound F") is quantitatively the chief secretory product of the human adrenal cortex [though Morris & Williams (467) have presented evidence that corticosterone is also present in peripheral blood in abundant amounts], most clinical studies have dealt with aspects of cortisol metabolism, which will therefore constitute the major portion of the following.

Cortisol.—There is general agreement that intravenously administered cortisol leaves the body rapidly (468, 469, 470), and is excreted mostly in the urine (468, 471, 472) with very little excretion into bile and no absorption via the thoracic duct (471). It may (473) or may not (468, 474) diffuse into

the cerebro-spinal fluid, and undergoes little or no alteration in the steroid nucleus (468). Cope and associates (475) have detected cortisol (by chromatographic methods) in ascitic, pleural, and amniotic fluid (476), and, like Wilson *et al.* (477) and Holley *et al.* (478), have been able to find cortisol or its metabolites in synovial fluid of steroid-treated patients with rheumatoid arthritis. The rate of disappearance of administered cortisol from the plasma has been variously reported to be unchanged (468, 479, 480) or changed (481) by the plasma level of cortisol.[4] Cortisol disappearance rate is delayed in hepatic cirrhosis (483, 484, 485), in the moribund state (486), and inconstantly in myxedema (323), while it is occasionally accelerated in thyrotoxicosis (323) and normal in Addison's disease in the "stress" of acute adrenal crisis (479, 480) and after epinephrine administration (487). Quantitative aspects of cortisol metabolism have been studied by Peterson & Wyngaarden (323) using trace quantities of 4-C^{14}-labeled cortisol. They estimate the normal miscible pool of cortisol to be 1.1–2.4 mg. with a volume of distribution of 8–17 liters, and the "endogenous cortisol turnover rate" to be 17–29 mg. per day, the miscible pool and turnover rate being increased by ACTH and decreased by prednisone administration. Their estimate of daily cortisol production is probably most closely approximated by the method of Norymberski (488), of all the clinical methods of urinary "corticosteroid" determination. One may postulate that this is the case because the Norymberski technic, unlike most others in clinical use, would measure steroid metabolites reduced at the 20 position, and would therefore include such compounds as the new steroids identified by Fukushima *et al.* (489) ("cortol," "cortolone") which, the authors claim, represent at least 30 per cent of the metabolites of cortisol. Interconversions *in vivo* have been shown to occur to a rather small extent (473, 490) in the absence of adrenal tissue (491).

Several methods for the measurement of nonconjugated plasma "17-OH-corticosteroids" (chiefly cortisol) in plasma have been used in clinical studies, and the subject has been reviewed by Bongiovanni & Eberlein (492). Most of the methods in wide use are based on the Porter-Silber reaction which is moderately specific for the 17,21-dihydroxy-20 keto-side chain, and therefore should detect cortisol, cortisone and compound S in an organic-solvent-extractable (i.e., free, nonconjugated) state. For practical purposes cortisol is probably the only steroid measured under usual conditions (492). Normal values have ranged from 3 to 28 μg. per cent (323, 335, 493 to 499). Migeon *et al.* have reported satisfactory agreement between values obtained by one of these methods (500) and by measurement of cortisol after paper chromatographic separation (501). Amounts of the same order of magnitude have been found by other technics [polarography (502), fluorescence (503), ultraviolet light absorption, and reaction with blue tetrazolium (476, 504)].

[4] Ely *et al.* have reported that Δ^1-cortisol (prednisolone) disappears more slowly from the plasma than cortisol (482).

The problem of diurnal variation of plasma and urinary 17-OH-corticosteroids has been studied by Migeon *et al.* (505), and DiRaimondo (506). Changes in levels of plasma 17-OH-corticosteroids under many conditions of disease, "stress" and ACTH administration have been reviewed in detail by Dodds and co-authors (10), and Bongiovanni & Eberlein (492). Nelson *et al.* have presented useful data on changes in plasma 17-OH-corticosteroid levels following the administration of various steroids orally and parenterally (507).

Since cortisol is in large part excreted in the form of conjugated metabolites [chiefly glucuronides (8, 468, 480)], it seemed a reasonable assumption that cortisol glucuronides "tetrahydro E" and "tetrahydro F" should be present in plasma also. This is apparently the case (468, 484, 485, 508, 509, 510). It is of interest that the slow rate of disappearance from plasma of administered cortisol in hepatic disease can be shown to be associated with a reduced rate of conjugate formation (484, 485). Brown *et al.* have shown that the essential defect may lie in disordered reduction of cortisol, which appears to be a necessary prior step before conjugation can occur (511). Peterson *et al.* have presented suggestive evidence that cortisol, but not certain other steroids, is defectively metabolized in hepatic cirrhosis (323).

Several investigators have studied the role of plasma and tissue proteins in the binding of steroids. In *in vitro* studies Westphal *et al.* showed that 2 to 10 per cent of cortisol was bound to and transported by human serum albumin (512). Levin *et al.* (513) found that rat liver, diaphragm, kidney, and spleen bound administered cortisol, confirming the protein binding shown earlier for other steroids as well as cortisol by Bischoff & Piehorn (514) and by Eik-Nes *et al.* (515). Levin and associates suggested that this affinity of protein for steroid might play a part in the rapid disappearance of cortisol from plasma, and that cortisol might act physiologically as a protein-steroid complex (513). Daughaday & Bremer have shown that free cortisol is loosely bound to plasma proteins, and that cortisol glucuronide is still less tightly bound (516). They suggest that renal mechanisms for disposal may involve tubular secretion and glomerular filtration (516), and Bongiovanni & Eberlein (517) reported that corticosteroid conjugates appeared to be more rapidly cleared by the kidney than free steroids.

As indicated above, there is abundant clinical and experimental evidence of the central role of the liver in the normal metabolism of steroids [see Lieberman & Teich (8)]. Effects of the kidney have also been studied. Wallace *et al.* (335), in a clinical study, showed that although urinary excretion of steroids (largely conjugated) in severe renal disease was often subnormal, plasma 17-OH-corticosteroids (measured as free corticosteroids) were generally within the normal range. Brown & Englert (511) found elevated plasma 17-OH-corticosteroid conjugates in uremic subjects. *In vitro* experiments by Lombardo *et al.* (518) revealed that an apparently "physiological" kidney perfused with steroids (including cortisol) was unable to effect steroid conjugation, while Ganis *et al.* were able to show that cortisol

incubated with kidney slices underwent reduction and also degradation of the side chain (519).

Biosynthesis of adrenal steroids.—The fundamental advances in the basic knowledge of the adrenal have allowed us to understand more thoroughly both the normal biogenesis in the adrenal cortex and the alterations which occur in certain of its diseases. The pioneer works of Hechter, Pincus, Samuels, Gallagher, Dorfman and Lieberman have laid down a structure of the *in vivo* synthesis and degradative metabolism of the steroid hormones. These mechanisms have been adequately reviewed by Hechter & Pincus (6), Dorfman & Shipley (7), and Lieberman & Teich (8). In brief, the sum total of these investigations has indicated a definite pathway of synthesis for steroids within the adrenal cortex, using cholesterol and acetate as the primary precursors. The steroids escape or are secreted into the circulation and are metabolized along well established pathways and excreted as urinary metabolites or degradation products. The metabolites of the steroids are so constant that the type of steroid actually secreted by the adrenal can be ascertained from the metabolites found in the urine. On the basis of urinary metabolites isolated from patients with various hyperadrenal states, Dorfman (520) has postulated possible underlying mechanisms of these diseases.

Biogenesis.—Cholesterol is found in high concentration within the adrenal cortex, and the administration of ACTH results in a prompt decrease in the concentration of this steroid within the gland. Consequently it had been thought that cholesterol must play an important role in the secretion of the adrenal steroids. Indeed, by the use of isotopically labeled cholesterol, it has been shown that this sterol is an important precursor of the various steroids synthesized within the adrenal. Three important changes are necessary: (*a*) the cleavage of the cholesterol side chain, (*b*) 3β-hydroxydehydrogenase, and (*c*) the hydroxylation at certain portions of the molecule. Very little is known about the enzyme systems involved in the cleavage of the side chain of the cholesterol molecule. The 3β-hydroxydehydrogenase enzyme is present in the adrenal and converts the delta^5 to a delta^4 configuration. However, this enzyme is not restricted to the adrenal gland but is found in the placenta, ovary and testis as well (521). Apparently this is the only enzyme system which has been studied which does not require molecular oxygen (522). There are a series of enzyme systems within the adrenal gland which are responsible for the hydroxylation at the 11, 17 and 21 carbon positions. The co-factors and requirements of these enzyme systems have been fairly well characterized by several different investigators. Progesterone is the obligatory precursor of the adrenal steroids. It has previously been shown by Bush (523) that the adrenal vein blood of different species of animals varies in the concentration of cortisol and corticosterone. The rodent adrenal vein blood contains a higher concentration of corticosterone than cortisol, whereas the adrenal vein blood of man contains the reverse proportions. The differences in the

ratios of these two steroids may depend upon the difference in the concentration of the 17-hydroxylating enzymes within the respective glands. Kass & Hechter *et al.* (524) have shown that after prolonged administration of ACTH to the rabbit there is an increase in the adrenal vein blood concentration of cortisol as contrasted with corticosterone, indicating that with adrenal hypertrophy there is an increase in the concentration of the 17-hydroxylating enzyme.

Studies with the use of C^{14}-labeled acetate have shown this substance to be an important precursor for the synthesis of adrenal steroids as well. Hechter & Pincus (6) have postulated as a result of calculations of specific activity that cortisol may be synthesized from acetate without using cholesterol as an intermediate. The interpretation of this is open to question but it is still possible that cholesterol may not be an obligatory precursor. Hechter & Pincus (6) found that whereas the conversion of C^{14}-cholesterol to corticoid is increased 1800 per cent by the addition of ACTH, the conversion of another precursor, progesterone, to corticoid is increased only about 17 per cent. With C^{14}-acetate, ACTH increased the conversion to corticoid by only 140 per cent. Consequently Hechter postulated that the alternative pathway of acetate conversion to corticoid, which does not involve cholesterol as a precursor, is not significantly increased by ACTH, and that in the absence of ACTH, synthesis proceeds primarily from acetate through the non-cholesterol pathway. When ACTH is present the cholesterol pathway is utilized as well. Since ACTH did not increase the conversion of progesterone to corticoid, it was claimed that its action (ACTH) appears to be primarily upon making another intermediary, namely pregnenolone, available for the adrenal enzymatic apparatus. What is secreted by the adrenal then depends upon the enzymes present in the gland. The role of ACTH in corticosteroid biosynthesis apparently is to facilitate the side chain scission of cholesterol.

Hyperadrenalism.—The demonstration of the biosynthesis of steroids has led to a better understanding of certain adrenal diseases. Several investigators have been involved in studying patients with congenital adrenal hyperplasia in an attempt to identify the basic steroidal abnormality in this condition; in fact, this condition has been called an "inborn error of steroid metabolism" (525). Since the administration of ACTH does not result in any increase in urinary or plasma corticoids, nor in sodium retention nor in fall in the circulating eosinophils, Bartter, Albright *et al.* (526) postulated that there is a difficulty in the synthesis of hydrocortisone in this condition and that adrenal androgens are being secreted more easily. Jailer (525), utilizing the schema of Hechter, postulated the existence of a block in the enzymatic synthesis of hydrocortisone from progesterone causing a "piling up" of one of the cortisol precursors, namely 17-hydroxyprogesterone. Bongiovanni (527) administered 17-hydroxyprogesterone and detected large amounts of pregnanetriol as the result of the administration of this steroid. Pregnanetriol is found in large concentration characteristically in congenital

adrenal hyperplasia. It was later shown that large amounts of 11-oxygenated 17-ketosteroids are found in the urine of some patients with congenital adrenal hyperplasia. The administration of 17-hydroxyprogesterone and 21-desoxyhydrocortisone to patients revealed urinary metabolites similar to those found normally in congenital adrenal hyperplasia. Consequently it was postulated (528) that in congenital adrenal hyperplasia there are varying defects in the hydroxylating enzyme systems which hydroxylate at the C 11, 17, or 21 position, resulting in a defective synthesis of hydrocortisone and the piling up of certain precursors. These precursors escape into the circulation and are metabolized along known patterns to steroids which are androgenic, which may be responsible for the virilism so characteristic of the disease. Dorfman (520) on the other hand claimed that the block is only at the 21 position and that the virilism is the result of a concomitant increase in the secretion of C^{19} androgens from the adrenal cortex.

Some few patients with congenital adrenal hyperplasia accompanied by virilism have, in addition, hypertension. Bongiovanni (529, 530) found no lack of C-21 hydroxylation but claimed that the defect may be in an inability of 11-hydroxylation with the production of 17-hydroxy, 11-desoxy-corticosterone and 11-desoxy-corticosterone. Evidence for this is the finding of tetrahydro S and tetrahydro DOC in the urine of the one patient that he studied. He postulated that the hypertension in this case was caused by the oversecretion of DOC by this pathological adrenal.

Aldosteronism.—The mineralocorticoid secreted by the adrenal cortex appears to be aldosterone. It has now been definite established that the salt-retaining factor found in the urine of patients with nephrosis is identical with the substance isolated from adrenal tissue [Luetscher & Wettstein *et al.* (531, 532)]. Subsequent to this the Basel group were able to synthesize aldosterone (533). The data obtained by Giroud *et al.* (534) would indicate that in the rat adrenal at least, the zona glomerulosa is the site of synthesis. A physico-chemical method for estimating the aldosterone content of biologic fluids utilizing two separate chromatographic procedures has been proposed by Neher & Wettstein (535, 536), whereas Liddle *et al.* (537) have proposed an elaborate biologic assay on adrenalectomized dogs. The latter assay is very sensitive and reproducible and has many advantages over the rat assay; however, it is costly.

Aldosterone differs from the other known adrenocortical steroids in that it is oxygenated at the C-18 position. Kahnt *et al.* (538) incubated C^{14} desoxycorticosterone with adrenal tissue and achieved a 48 per cent conversion to aldosterone. However, Rosemberg *et al.* (539) could not confirm this but did demonstrate that progesterone could act as a precursor for aldosterone. These results demonstrate the existence of a C-18 hydroxylase in adrenal tissue.

The factors regulating the secretion of aldosterone by adrenal tissue are still not clearly defined. Apparently ACTH has but a minor trophic effect. Singer & Stack-Dunne (540) and Farrell *et al.* (541) could detect minor al-

terations in the aldosterone content of rat adrenal vein blood after hypophysectomy and ACTH administration, and Luetscher *et al.* (542) obtained similar results in man. The regulation of its secretion is apparently bound up with certain homeostatic influences in salt and water metabolism. Luetscher and his co-workers (542, 543, 544) showed an inverse correlation between the concentration of urinary sodium concentration and the aldosterone values. The aldosterone values are high when the urinary sodium ion concentration is low, except in polycystic renal disease or in congenital adrenal hyperplasia where the steroid values may be normal or even elevated in the presence of sodium loss. Rosenfeld *et al.* (545), using surviving beef adrenals, showed that changing the Na/K ratio of the perfusate from 42/1 to 5/1 resulted in a marked increase in the output of aldosterone. Laragh & Stoerk (546), as a result of data obtained in both the dog and man, maintain that the concentration of serum potassium is the powerful direct or indirect stimulus to aldosterone secretion and that the increase in concentration of this steroid found as a result of sodium restriction is mediated by an alteration in serum potassium or Na/K ratio. On the other hand, Beck *et al.* (547) have claimed that alterations in aldosterone secretion occur in response to changes in the volume of extracellular fluid. They administered vasopressin to two normal subjects and produced water retention which was accompanied by an increased urinary excretion of sodium and a fall in the serum sodium. Upon cessation of the vasopressin administration there was a diuresis of water, a loss of body weight, and a decrease in urinary sodium excretion together with an increase in the aldosterone values. Bartter & co-workers (548) have obtained similar results. The biologic effects of aldosterone in both experimental animals and in human subjects have been extensively reviewed by Gaunt (549) and by Mach (550, 551).

Luetscher & Curtis (552) have reviewed the clinical conditions in which the urinary aldosterone values are excessive. They are situations in which the sodium content of the urine is low and usually edema is present. Elevated urinary aldosterone values are found in nephrosis, cardiac failure, cirrhosis associated with ascites, and toxemia of pregnancy. However, no claim is made for the aldosterone as an etiologic agent. Venning & Dyrenfurth (553) more recently have found increased aldosterone values in normal pregnancy which were as elevated as those previously described for toxemia, although in the latter pathologic condition the concentration of the "free form" as contrasted with the "conjugated" form is high.

Genest *et al.* (554) claim to have detected increased amounts of aldosterone in the urine of patients with both benign and malignant hypertension. These findings were apparently independent of the salt content of the diet and edema. However, this can be a reflection of the renal status. Prader *et al.* (555) showed normal or slightly increased values of the urinary salt-retaining factor in infants with congenital adrenal hyperplasia and the salt losing syndrome, the values of aldosterone in a child in whom there was

a spontaneous remission being greatly elevated. They present this as further evidence that an unidentified sodium-excreting adrenocortical factor is secreted in this condition, and that in certain patients the salt losing syndrome is compensated by a secondary increase in aldosterone secretion.

Since the first demonstration of an aldosterone-secreting adrenocortical tumor by Conn (556) several other cases of "primary aldosteronism" attributable to tumors have been reported [Mader & Iseri (557); Foye & Feichtmeir (558)]. The pertinent clinical symptoms were those of extreme weakness whereas edema was not striking. The serum electrolyte pattern was characterized by markedly depressed potassium and elevated CO_2 levels.

Adrenal suppression.—Suppression of pathologic adrenal activity by the administration of amphenone (1,2 bis (*p*-aminophenyl) 2-methyl-propane-1-dihydrochloride) has been described by Hertz *et al.* (559, 560). The administration of large doses of amphenone to at least two patients with adrenal carcinoma has resulted in a decrease in 17-ketosteroid excretion in both urinary and plasma 17-OH-corticosteroid and increased glucose tolerance [Thorn *et al.* (561)]. It is ineffectual in the presence of adrenal hyperplasia. Renold *et al.* (562) administered it to normal individuals and found a decrease in the aldosterone excretion values. Tullner and co-workers (563) reported that the administration of amphenone to the hypophysectomized dog resulted in a fall in the 17-OH-corticoid output in the adrenal vein blood and that it reduced the response to ACTH. In normal dogs on a similar regimen there was a temporary fall in corticoid excretion. Apparently amphenone inhibits adrenal biosynthesis directly.

Chromosomal Sex Determination

The genetic determination of sex depends upon the inter-reaction between the autosomes and the sex chromosomes. Apparently in the human there are 46 autosomes with two sex chromosomes. The distribution is such that in the female there are two X chromosomes and in the male the X and Y chromosomes, the latter being a vestigial chromosome. More recently a dispute has arisen as to the relative roles of the genetic influences and those of the embryonic gonads in the differentiation of the genital duct and the external genitalia. Jost (564, 565), and Raynaud & Frilley (566) have demonstrated that removal of fetal gonads leads to the development to female genital ducts and female external genitalia, irrespective of the genetic makeup of the fetus. In view of these results it was concluded that the fetal testis counteracts the inherent tendency of the fetus to feminize. Barr and his associates (567, 568, 569) have noticed differences in the chromatin pattern in the nuclei of the resting somatic cells between males and females, whereas previously the chromosomal counts could be done only in dividing cells usually found in the gonads. Barr has shown that in practically all cells one of the X chromosomes remains intact within the nucleus, giving the appearance of another peripheral nucleolus in the fe-

male. This structure apparently is absent in the male nucleus. Detectable differences have been found in skin biopsies, vaginal smears [Carpentier (570), Carpentier *et al.* (571)], in peripheral blood smears [Davidson & Smith (572); Sun & Rakoff (573)], and in buccal mucosa [Marberger *et al.* (574)]. In all the chromatin pattern is different in the male and female resting cells.

This technique was soon applied by many investigators to various clinical conditions where abnormalities in the sexual spheres were noted, and the results have increased our understanding of such abnormalities. For example, it is known that in both the male and female pseudohermaphrodite (575, 576) corresponding chromatin patterns are observed. Polanni *et al.* (577), Decourt *et al.* (578), Grumbach *et al.* (579), and others, have demonstrated that in about 80 per cent of patients with the syndrome of ovarian agenesis or dysgenesis, there is a male chromatin pattern, in spite of the fact that outwardly fairly normal female secondary sex characteristics are present. In other words these are individuals who are chromosomal males, but they have developed along feminine lines because of the atrophy of the fetal gonad. This is reminiscent of the experiments of Jost (564, 565) who claimed that intrauterine castration of the fetal rabbit beginning at a stage when the testes can be identified histologically, but before the genital tract is differentiated, results in the establishment of female secondary sex characteristics (Müllerian duct system). The fetal testes are necessary for the organization and development of the Wolffian duct system; thus, ovarian dysgenesis has been interpreted in the light of these animal experiments.

In addition, in several male patients with the so-called Klinefelter syndrome the female sex chromatin pattern has been identified [Plunkett & Barr (580); Bradbury *et al.* (581)]. This finding is much more difficult to explain in the light of the experimental evidence. It is entirely possible that the chromosomal pattern in this condition is XXY and that this combination of sex chromosomes in the human gives rise to the male phenotype. Under these conditions the resting cell chromatin material would look more like the female sex pattern, since the Y chromosome cannot be seen. Although Barr and his collaborators (569) have cautioned about generalities based solely on the sex chromatin material, many investigators have reclassified the various types of sexual abnormalities in the light of this finding. Most recently Bunge & Bradbury (582) have demonstrated spermatogenesis in a testis biopsy of a patient with the Klinefelter syndrome, in spite of the fact that the resting cells demonstrated the typical female chromatin pattern. This finding of spermatogenesis would tend to contradict the female sex chromatin finding. Consequently, we must conclude that at the present time it is too premature to equate the sex chromosome with genetic maleness or femaleness.

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ALLERGY AND IMMUNOLOGY[1,2]

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One of the most striking characteristics of human allergy is the diversity of its manifestations. In a single organ allergic injury may manifest itself in many different ways, as for example, in the skin by varying degrees and combinations of purpura, erythema, edema, vesiculation and scaling. No single mechanism has been advanced which will satisfactorily explain all of these diverse phenomena, and indeed there is little agreement as to the criteria by which their allergic nature is determined.

This paper represents only one of the many viewpoints which are tenable in this complex and controversial field. Instead of attempting to cover all of the recent work pertaining to allergy and immunology, only those papers will be discussed which relate historically or experimentally to the limited number of topics covered. The chief feature of the paper is the concept of antibodies as a diverse group of naturally occurring proteins, rather than new species of protein molded on antigen templates. The evidence is reviewed which indicates that antigens selectively stimulate the production of those natural proteins for which through chance alone they have the greatest affinity.

Definition of Allergy

Some concept of hypersensitivity must have existed as far back as the first century B.C. when Lucretius wrote that "what is food to one man may be fierce poison to others" (77). The more definitive term "allergy" was proposed by von Pirquet (116) in 1906 to describe the altered reactivity of an organism that results from contact with such diverse substances as tubercle bacilli, small pox vaccine, toxins and serum. Von Pirquet's definition was broad in that it included both hypersensitivity and hyposensitivity, but on the other hand it was limited to those instances of hypo- and hyper-sensitivity which resulted from exposure to the reactant or allergen. Such a term could not be made to fit easily into any orderly system of nomenclature, and few writers have continued to use it in the original sense. Many texts now consider allergy as covering any form of hypersensitivity (33, 112), and thereby lose both the broad and the limiting concepts that von Pirquet attached to the word. Other writers (23, 82) deviated still further from von Pirquet's

[1] The survey of literature pertaining to this review was completed in August, 1956, and was aided by grants A-358 and C-2352 from the National Institutes of Health, United States Public Health Service.

[2] The following abbreviation has been used in this review: GSU (globulin synthesizing unit).

definition by using allergy to describe a certain type of reaction (e.g. asthma, rhinitis or urticaria) rather than the capacity to react. In this paper allergy is considered to pertain to hypersensitivity only and not to hyposensitivity. Also included, however, is von Pirquet's limitation of the term to reactivity altered by exposure to the allergen. More important than the exact wording of the definition are the general concepts of disease that give it meaning. The following considerations seem important to this writer: (*a*) The term "allergy" should not be used to indicate both the mechanism by which reactivity is induced and the form of the ultimate response. When injured, a given cell can respond in only a limited number of observable ways (100), e.g. erythrocytes tend to hemolyze and muscle cells contract, whether the stimulus be physical, chemical or an antigen-antibody reaction. The observed form of the reaction cannot in itself be an indication of the mechanism of injury. Since more definite terms are available to describe tissue and cellular reactions, it seems preferable to use the term "allergy" to indicate that the production of some intrinsic agent of injury, the antibody, was induced as a result of previous exposure to the allergen. (*b*) If possible, terms such as "allergy" should not be used to express unproven concepts (25) or to characterize clinical conditions of obscure origin. For example, the restriction of the term "allergy" to the wheal and erythema type of hypersensitivity implies that such reactions have a basically distinct mechanism. A result of this practice is that a large number of terms such as "atopy," "parallergy," "hyperergy" and "pathergy" must be coined to describe a particular type of reaction, each based on a different concept of the relations between various hypersensitivity states. (*c*) Any definition of allergy should fit in with a general classification of related conditions. If allergy is considered as a particular type of reactivity, the definition of allergy should be so formulated that other terms may provide an orderly coverage of all types of reactivity.

For example, allergic reactions may be profitably contrasted with toxic reactions. The latter are generally considered the results of a specific reactivity which is approximately the same in all members of the same species. Hypersensitivity may be considered to indicate a reactivity that is more than toxic, i.e. any specific reactivity of one individual which is substantially greater than that found in a majority of the members of the same species. According to this system of nomenclature, which will be used here, allergy is defined as hypersensitivity which is acquired through exposure to the specific reactant (allergen) or to a substance closely related to it. The use of the term "allergy" as a subdivision of hypersensitivity implies the existence of non-allergic hypersensitivities. An example of the latter is the hemolysis occurring in a small percentage of Negroes fed primaquine or related drugs (8, 9,). Through a variety of experiments including passive transfer of chromium-labeled red cells, Dern *et al.* (26) have demonstrated that this hypersensitivity is attributable to an inherited abnormality in the metabolism of the red cells of sensitive individuals.

In addition to inherited and allergic origins, hypersensitivity can arise as the result of disease or fortuitous circumstance. A striking example of this is the hypersensitivity to histamine occurring in mice following an injection of *Hemophilus pertussis* (86). A discussion of this phenomenon is beyond the scope of the present review.

Relation of Allergy to Antibodies

In certain forms of human allergy, little doubt exists of the importance of circulating and tissue antibodies to the production of symptoms. In many other allergic states, however, circulating antibodies have not been conclusively demonstrated, but the presence of some specific agent (circulating or otherwise) is strongly indicated by the specificity of the reactivity. Tuberculin reactions are an example of allergy in which a question remains in regard to the existence of a circulating antibody responsible for the reaction (95).

Recently, Cole & Favour reported the passive transfer of tuberculin hypersensitivity with an alpha globulin fraction of the serum of a sensitized guinea pig (21). The reason given for the success of this transfer (in contrast to previous failures) was the separation of the sensitizing antibody in the alpha globulin fraction from a blocking antibody in the gamma globulin. This interpretation leaves a number of important questions unanswered. If antibodies in the gamma globulin fraction can block tuberculin reactions, it is difficult to understand why cells from spleen or peritoneal exudates serve so well for the transfer of tuberculin reactivity (17, 19, 70). These cells have been used to transfer many diverse antibodies (18, 42, 43, 97, 109), some of them almost certainly in the gamma globulin fraction.

Experiments with agammaglobulinemia would seem ideally suited to resolve this problem, but to date the results have not answered the questions raised by Cole & Favour. Good reported that patients with agammaglobulinemia did not develop a spontaneous delayed reactivity to streptococcal allergens as often as normal people in the same age group (38). This finding cannot be interpreted as implicating gamma globulin as the agent of delayed allergic injury for at least three reasons: (*a*) The defect in agammaglobulinemia may involve more than gamma globulin synthesis. While plasma cells are almost entirely absent in this disease, other cells appear to be affected (36). (*b*) Gamma globulins may not be directly involved in the allergic reaction, but their presence may accelerate the development of delayed allergy. This is suggested by Pappenheimer's finding that animals passively immunized with precipitating anti-egg albumin serum developed a delayed type reactivity to egg albumin several weeks after an injection of this antigen (85). (*c*) In contrast to their inability to develop circulating antibodies (14) and to develop delayed allergy spontaneously, patients with agammaglobulinemia may be actively sensitized to BCG (Bacille Calmette-Guérin vaccine) and 2-4 dinitrofluorobenzine (37, 68, 90). Delayed reac-

tivity to the latter could be transferred to a nonsensitive recipient by the subcutaneous injection of viable white blood cells but not with a large volume of serum (37).

The development of delayed reactivity in an agammaglobulinemic patient might be due to the relatively small amounts of gamma globulin synthesized by these patients if only very small amounts of antibody are required to give maximum reactivity. A similar assumption seems adequate to explain the relatively good immunity to viral diseases which develops in the agammaglobulinemic patient (36). In the case of tuberculin allergy, however, quantitative factors cannot explain both the difficulty encountered in the transfer of the allergy with a large volume of serum and the ease of transfer with relatively small numbers of leucocytes.

The results reported by Cole & Favour and those with agammaglobulinemic patients do not answer the question as to the nature of the specific agent of tuberculin allergy. They do suggest, however, that the distribution of this specific agent in the various body compartments is different from that of gamma globulin and that its production involves some cell beside the plasma cell.

Definition of Antibody

If tuberculin allergy is due to a humoral agent which differs from gamma globulin in production and distribution, should this agent be called an antibody?

According to the antigen template theory of antibody production (4, 11, 16, 45, 46, 78, 84, 87), antibodies are normal gamma globulins which have a configuration complementary to antigen as a result of being synthesized in relation to an antigen template. The unitarian theory of antibodies (13, 117) gave support to this view by stating that there was formed for each antigen only a single antibody. According to both of these concepts as originally formulated, antibodies differ from each other only in the configuration of the reactive site, a small fraction of the total surface of the molecule. Increasing evidence of marked differences between the physico-chemical properties of antibodies has required modifications of both the antigen template and unitarian theories. Raffel reviews the evidence of antibody diversity and suggests that different cells may take part in producing molecules with these various characteristics (94). Antibodies to the same as well as a different antigen have been found to vary in (*a*) physico-chemical property (60, 66, 93, 106) including N-terminal amino acid sequence (91), (*b*) ability to produce secondary reactions such as hemolysis (105), fixation of complement (50, 65), skin sensitization (64), agglutination (51, 115), precipitation (48) and Arthus reactions (7, 62), (*c*) avidity for the injected antigen (6, 57), (*d*) cross reactivity with related antigens (54, 69), (*e*) rate of metabolism (110), and (*f*) distribution between blood and tissues (110).

If recognized antibodies vary in all these properties, can any of them be used as a criterion for defining antibodies? Pillemer has stated that properdin is not an antibody because of the dependence of its reaction with zymosan on magnesium, complement and temperature (88, 89). However, immune hemolysis is known to be critically dependent on magnesium (74) and temperature (72, 80). Antibodies vary widely in their reactions with complement. Soluble antigen-antibody complexes can be precipitated by complement (79, 113). Nonprecipitating antitoxin, on the other hand, fixes complement little or not at all (65).

The only properties common to all antibodies are (*a*) their protein nature, (*b*) an increased production following exposure to antigen, and (*c*) affinity for the antigen. In these respects, properdin is an antibody (71). So, almost certainly, is the intrinsic agent responsible for tuberculin allergy.

Production of Antibodies

If allergy is due to the presence of antibodies, then the problem of allergic sensitization is largely that of antibody production. The site of antibody formation from the morphologic standpoint has been adequately covered in recent reviews by Harris (44) and Kuhns (67). From the standpoint of the biochemical mechanism involved, three basically different theories of antibody production have been described. In somewhat over-simplified terms, these three theories are: (*a*) Antigen template theory (4, 11, 16, 45, 46, 78, 84, 87). The antigen itself becomes an integral part of the globulin synthesizing unit (GSU) and is in fact the template through which the antibody receives a complementary configuration. (*b*) Adaptive enzyme theory (15). The antigen induces a change in existing GSU and at the same time induces them to produce antibody and to replicate. (*c*) Natural selection theory (29, 58). The antigen selects from a wide variety of existing GSU those with which it has greatest affinity and induces them to produce antibody and to replicate.

The antigen-template theory is probably the most widely held at this time. It was first advanced at a time (1930) when the unitarian hypothesis had reached wide acceptance. When it became possible to demonstrate the identity of agglutinin and precipitin (49), it seemed reasonable to assume that antibodies varied only in specificity. The demonstration of antibodies against artificially synthesized chemical groups conjugated to protein (69) seemed to rule out Ehrlich's concept of a natural receptor. It was thought that only by receiving a direct impression of the antigen could gamma globulin molecules acquire an apparently unlimited number of configurations.

Changing concepts of unity and specificity of antibodies have required modifications in the antigen-template theory. Antibodies to the same antigen with varying cross reactivity to related antigens have been ascribed to variations in the size and area of the template (94). "Complete" and "in-

complete" antibodies have been explained by a difference in the number of reactive sites. Differences in physico-chemical properties of antibodies were thought to arise from the production of antibodies by different cells. Varying degrees of avidity between antigen and antibody were said to be due to varying "adaptation" of the antibody molecule to the antigen template (47).

Burnet was impressed with the gap that had developed between immunology and existing knowledge of biological processes (15). Nowhere in nature could an analogy be found to the concept of an antigen template. His adaptive enzyme theory was based on a model of bacterial enzyme formation. However, there is now considerable doubt that adaptation in bacteria occurs through a modification of enzymes as pictured by Burnet. Most authorities now use the term "enzyme induction" and hold that this type of enzyme synthesis involves the induction of inherited enzyme synthesizing units (83, 102).

Striking similarities exist between antibodies and inductive enzymes. Both are relatively large protein molecules (96) synthesized *de novo* (39, 40, 41, 52, 109) (i.e. not from protein precursors). Both have a more or less specific affinity for the substrate or antigen with which they react and by which they are induced. Inducer (which may have a configuration slightly different from the substrate or antigen) is required for both induction and continued production. With both enzymes and antibodies "memory" effects have been demonstrated (83).

A concept of antibody production as an induction of existing GSU is remarkably similar to Ehrlich's side-chain theory which was widely held more than 40 years ago (29). Ehrlich thought that antibodies derived from certain cell receptors or "side-chains." Antigens, by combining with those receptors with which they have natural affinity, induced their overproduction. Excess receptors were released into the circulation as antibodies. Jerne has recently proposed a "natural selection theory" to describe a basically similar concept (58). The term "natural selection" implies that adaptation of the individual occurs by selection from a multitude of existing processes much as adaptation of the species occurs largely through a natural selection of existing individuals.

The greatest objection to Ehrlich's side-chain theory was the apparent specificity of antibody for synthetic haptenes. It did not seem possible that a different natural receptor existed for every conceivable chemical group. However, changing concepts of specificity have reduced the force of this argument. Because of the large number of cross reactions now known to exist (27), it is no longer necessary to postulate an unlimited number of possible antibodies. Haurowitz has recently estimated that the total number of different antibodies may be less than 50,000 (47). Specificity is probably nothing more than a high degree of affinity, and affinity between naturally

occurring substances is common in nature. The action of enzymes is based on an affinity for the substrate. Toxins (3) and viruses (5) may have a highly specific affinity for cells with which they have had no previous contact. Penicillin (28) and isoniazid (63) have affinity for bacteria sensitive to their action. By means of an unusually sensitive test, Jerne has demonstrated the existence in rabbits of natural antibodies to a bacteriophage with which a previous contact could not have been made (59).

It is reasonable to suppose that when an antigen containing a synthetic chemical group is exposed to a large heterogeneous population of globulin molecules, some of these molecules through chance alone will have an affinity for the new configuration. The degree of affinity for antigen of randomly selected globulin molecules should vary with a normal distribution. If the number of different globulin molecules is large enough, there should be a few which have a high degree of affinity for any conceivable chemical grouping. Any mechanism of selectively multiplying those with high affinity will result in the production of "antibodies." In contrast to the antigen-template theory which is based on the unity of antibodies, the natural selection theory is necessarily based on a concept of their diversity. According to the latter concept, antibodies are found in the globulin fraction of serum instead of in the albumin fraction because of the greater natural heterogeneity of the globulin.

Burnet & Fenner have listed four essential immunologic observations which are not satisfactorily accounted for by the antigen-template theory (15). To this, Jerne has added a fifth (58). These five are: (*a*) the specific anamnestic response; (*b*) the increasing avidity of the antibody formed as immunization continues; (*c*) the exponential rise in circulating antibody; (*d*) the continued production of antibody for long periods, and (*e*) the dominant part played by the surface of particulate antigens in determining the specificity of the antibody molecules produced.

To this list should be added the remarkably rapid rate at which antibody synthesis can occur. It may be recalled that it was experiments by Topley which ruled out the incorporation of antigen into the reactive site of antibody (111). Calculations based on these experiments have indicated that the injection of a single molecule of antigen gave rise to an amount of antibody globulin sufficient to agglutinate 600 bacteria (53) or 100,000 antibody molecules per second per bacterium injected (58). This represents nearly one antibody molecule per second per molecule of antigen even if the unlikely assumptions are made that the entire bacterium is antigen and all the antigen is utilized for the production of antibody. Similar calculations can be made from results obtained by the single injection of sheep red cells into rabbits (107). In three rabbits the mean antibody response to a single injection of one-fortieth of a unit of sheep cell suspension per kg. body weight was seven Forssman combining units per ml. The antibody in one ml. of

serum was sufficient to combine with 280 times the amount of antigen injected per kg. Assuming 80 ml. globulin space per kg. and assuming further that this antibody was produced within a 48-hr. period, it follows that one antibody molecule was produced every eight sec. for each Forssman combining site injected. If consideration is given to the facts that under these conditions approximately 1 per cent of the antigen going to the spleen (56) gives rise to 90 per cent of the antibody (108), the rate of antibody production becomes nearly 10 molecules per sec. per template. Since it is doubtful that more than a small fraction of this antigen is taken up by the antibody-producing cell and is still present at the time of maximum antibody production, the rate of antibody turnover on the hypothetical antigen template must be high indeed.

Experiments using isotopically labeled antigen might succeed in measuring more definitively the maximum rate of antibody production relative to the amount of antigen remaining. It seems likely that such experiments will rule out an antigen template as a theoretical possibility for three reasons: (*a*) protein synthesis is a relatively slow process in comparison to other enzymatic reactions (10); (*b*) the release of antibody from antigen under physiologic conditions is measured in minutes and hours rather than seconds (103); and (*c*) the avid antibody of the secondary response is produced more rapidly from less antigen than the relatively non-avid antibody of the primary response. This is opposed to the relatively slow release of avid antibody that would be predicted if an antigen template is assumed.

Burnet & Fenner (15) have postulated a "self marker" enzyme system present in every antibody-producing cell which recognizes autologous proteins and prevents the production of auto-antibody. This marker system must be established in early fetal life in order to account for the permanent refractoriness to antigens injected at this time. As Jerne has indicated (58), the natural selection theory gives a simpler and more definitive explanation for the absence of auto-antibodies. If these proteins or their synthesizing units are eliminated during fetal life, they will not be available later for selection and multiplication.

While Ehrlich and Jerne's theories agree in considering antibody formation as a process of natural selection, they differ considerably in the mechanism by which this selection occurs. Ehrlich considered that selection occurred as a result of natural affinity between antigen and cellular receptors. Jerne, on the other hand, suggests that antigen, by combining with free receptors (natural antibodies), draws the latter into appropriate cells where they are replicated. Thus, according to Jerne, the basis of replication is an extracellular protein, whereas according to Ehrlich a replica is made of some intrinsic cellular unit. The latter hypothesis is preferable for at least two reasons: (*a*) The cellular hypothesis is compatible with current concepts that the configuration of a protein molecule is determined solely by information

contained in the hereditary units of the cell, the nucleic acids. Jerne's hypothesis, the antigen-template theory, and the adaptive enzyme theory, all require that substances absorbed from outside the cell may carry configurational information to the synthetic processes of the cell. Within the limit of present knowledge, even the highly specific hormones govern only the rate of the predetermined metabolic processes of the cell; (*b*) Available experimental evidence points to the cell as the basis of the specific anamnestic response. When cells from the spleen or peritoneal exudates of an immunized animal were transferred to a normal animal, the recipients gave a prompt or anamnestic response to the injection of antigen (97). Transfer of serum from an immunized to a normal animal has been shown to suppress rather than accentuate the subsequent antibody response (107). To explain this discrepancy, Jerne suggests that an animal can distinguish between his own globulin and that of another member of the same species. This is a feat that antibody-producing systems have never been shown to accomplish, and Jerne's explanation does not account for the successful transfer of sensitization with cells.

The process of natural selection requires the selective multiplication of a few species out of a diverse population. As a working hypothesis it is tempting to consider that one of the multiplying units in the antibody response is the cell itself. According to this hypothesis, only those cells are selected for multiplication whose synthesized product has affinity for the antigen injected. This would have the disadvantage of requiring a different species of cell for each species of protein produced, but would not increase the total amount of configurational information required of the hereditary process. Three experimental observations may have bearing on this question. (*a*) The time required to sensitize an animal for a maximum anamnestic response is usually 30 days or more. This suggests that multiplication of cells is required rather than multiplication of subcellular units. The latter is a much more rapid process which may be important in the primary response. (*b*) Sensitization once established persists for a long time. This suggests the persistence of an already differentiated cell type. It might be expected that a multipotential cell would revert to the presensitized state after a few cell divisions performed in the absence of antigen. (*c*) The protein produced by the rapidly reproducing myeloma cells is remarkably homogeneous. Putnam suggests that in an individual case there is massive production of one globulin randomly selected from the family of normal globulins (92).

Measurement of Antibody

Since it is not possible to accept as proved any of the above described theories of antibody production, it seems profitable at this time to consider the implications of these theories to the problem of antibody measurement.

Antibody determinations may be divided into two general classes: first

stage reactions, which are based directly on the union of antigen and antibody, and second stage reactions, which measure some secondary effect of this union. If for each antigen there is only a single antibody formed, then the distinction between these two types of determinations is not important. Any method of measuring antibody, if sufficiently accurate and reproducible, would give a relative measure of the antibody content of a serum under these circumstances. The major consideration would be the specificity of the antibody being measured, since it is well established that differences in specificity may have a profound effect on the observable manifestation of the antigen-antibody reaction.

If, however, the antibodies in an antiserum are diverse in physicochemical property such as size, shape, valence, charge, and affinity for the same antigen, it is also likely that they are different in the capacity to initiate second stage reactions. The fact that the same antibodies can precipitate, agglutinate, and fix complement does not prove that all the antibody molecules present perform each function with equal efficiency. Nor does the concept of diversity necessarily imply (as it did to Ehrlich) that there is for each antigen an agglutinin, a hemolysin, a precipitin, or a skin-sensitizing antibody. Second stage reactions are probably only one result of a complex series of competing reactions. It would be surprising if the gross physicochemical property of the antibody molecule played no role in determining the outcome.

In order to distinguish between the divergent concepts of unity or diversity of antibody, it is necessary to measure the primary reaction between antigen and antibody. By comparing the capacity of an antiserum to combine with antigen with its capacity to agglutinate, precipitate, or hemolyze, it should be possible to measure their relative efficiency in performing these functions.

Only a limited number of techniques have been developed for studying the primary antigen-antibody reaction. These all involve the measurement of antigen-binding by antibody under certain fixed arbitrary conditions. If this measurement is made under two or more different concentrations of antigen or antibody, it is frequently possible to measure the avidity of the antibody involved. This avidity may be expressed in terms of its counterpart, i.e. reversibility or dissociation constant.[3]

Probably the earliest measure of antigen-binding capacity was made by a determination of diphtheria toxin neutralization (99). Although the

[3] The following formulas for the dissociation constant were derived by Farr (32).

$$K = \frac{(Ag)\cdot(Ab)}{AgAb} = \frac{(S)(B - P)}{P}$$

If the free antigen (S) and bound antigen (P) are known under two different concentrations of total antigen, the two constant unknowns, K (dissociation constant)

test depends on a biologic assay of total and unbound toxin, this assay is precise. It is significant that this test has permitted the demonstration of antibody diversity with respect to avidity (6, 57), physico-chemical property (66), precipitation, complement-fixing capacity, and skin-sensitizing ability (64, 65).

Another test of antigen-binding is haptene equilibrium dialysis, which was used by Eisen & Karush (30). Haptene is allowed to equilibrate through a dialysis membrane between saline on one side and antiserum on the other side of the membrane. The increased concentration of haptene on the antibody side is a measure of the haptene bound by antibody. The concentration of haptene can be measured if it is labeled with a dye or radioactive isotope.

It is apparent from the two examples given that the measurement of antigen-binding requires the separation of free antigen from bound antigen. In the first instance this is accomplished because free antigen is toxic and bound antigen is not. In the second instance only the free antigen passes through the dialysis membrane.

A similar measurement can be accomplished with any antigen-antibody system if the following conditions obtain: (*a*) the antigen is labeled to a high degree of specificity; (*b*) free antigen can be separated from bound antigen; and (*c*) the equilibrium is not disturbed by the process used for the separation.

These conditions appear to have been fulfilled by the technique described by Farr for I^{131} labeled bovine serum albumin (32). In this case antigen

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and B (total antibody valences) may be obtained by the solution of two simultaneous equations, giving:

$$K = \frac{P_1 - P_2}{\frac{P_2}{S_2} - \frac{P_1}{S_1}} \quad \text{and} \quad B = \frac{PK + SP}{S}$$

An alternative solution is to determine by interpolation or extrapolation the point of half saturation of antibody, i.e. the concentration of free antigen at which half the maximum antigen binding takes place. Under these conditions $P = B/2 = B - P$, and $K =$ the concentration of free antigen (S). These formulas are valid only in the region of considerable antigen excess where it may be assumed with minimal error that no more than one antibody molecule is bound to a single antigen molecule. The latter formula is similar to the Michaelis-Menten constant used for enzymes.

If it is desired to vary antibody concentration as well as antigen, the formula becomes only slightly more complex. In this case,

$$K = \frac{T_1P_1 - T_2P_2}{\frac{T_2P_2}{S_2} - \frac{T_1P_1}{S_1}}$$

where T is the reciprocal of relative antibody concentration.

bound by antibody globulin (but not free antigen) is precipitated by 50 per cent $(NH_4)_2SO_4$. With bacteria and cells, measurement of antigen-binding is more difficult because the antigen is at once both insoluble and impure. The problem of antigen purification alone is considerable. Before such antigens can be used to measure antigen-binding, they must be labeled and a process developed for separating free and bound antigen. A partial solution to this problem has been made through an alternative approach, that of labeled antibodies (104). The antibody is labeled with I^{131} and separated from other labeled proteins by a process of absorption and exchange elution. Since it is not practical to so label and separate every antiserum to be studied, antigen-binding is measured indirectly, i.e. by means of the inhibition of the uptake of a standard labeled antibody preparation.

The Mechanism of Allergic Injury

Allergy may be considered as an acquired mechanism of cell injury. The chief characteristic of the response is its diversity. In some instances, as for example rheumatic fever, a complex response pattern is highly specific for a single allergen. At the other extreme, anaphylaxis in the guinea pig gives the same characteristic symptoms for a wide variety of different antigens.

The quantity of allergen required to produce a reaction varies over an extremely wide range, not only from allergen to allergen, but with the same allergen from individual to individual. In human skin sites passively sensitized with serum from a penicillin-sensitive individual, 0.00001 μg. of penicillin may be sufficient to produce an immediate reaction (22). Routine intradermal skin tests to detect ragweed allergy employ less than 0.01 μg. extract nitrogen because larger doses involve a risk of an occasional systemic reaction. Since only a small fraction of the total nitrogen in the ragweed extract represents the active allergen, the actual amount of allergen injected may be considerably less than 0.01 μg. On the other hand, 160 μg. egg albumin nitrogen injected intravenously were necessary to produce fatal anaphylaxis in a guinea pig (61), a highly sensitive animal less than 1 per cent as large as man. Similarly, local Arthus reactions in the rabbit require an injection of approximately 50 μg. antigen N and a concentration of circulating precipitating antibody N of 50 μg./ml. or more (24).

Although the diversity of allergic response suggests that these various reactions are due to a viariety of mechanisms, the particular mechanism involved in any case probably depends largely on only three major components of the reaction: the allergen, the antibody and the cell. The allergen varies in physico-chemical property, affinity for cells and other tissue components, valence, distribution, rate of metabolism, toxicity of breakdown products, and ability to stimulate antibody production. The antibody varies in physico-chemical properties, valence, affinity for antigen, distribution in

the body and rate of metabolism. Since the resulting antigen-antibody reactions vary in their secondary manifestation such as hemolysis or complement fixation, it is highly probable that they also vary in their ability to produce any type of cell injury. Cells, on the other hand, vary in the threshhold of response to injury, and in the degree and quality of symptoms by which that response is manifest.

There are very few allergic reactions in which the mechanism of injury is known in any detail. Enough information is known concerning a variety of mechanisms, however, to bear out the above concept of diversity. Antigen-antibody reactions taking place *in vivo* vary in their relationship with the cell. In general, the less intimately the cell participates in the reaction, the more antigen and antibody are required to produce cell injury. For example, antigen-antibody aggregates under certain circumstances may physically obstruct capillaries. That such a mechanism is involved in the Arthus reaction in the rabbit is suggested by the correlation between the reactivity of the animal and a high concentration of circulating precipitating antibody (7, 62). A similar mechanism cannot be involved in more sensitive reactions requiring only a small fraction of a microgram of allergen.

Antigen-antibody reactions may affect the cell indirectly in other ways. The reaction may activate an extracellular enzyme system which injures cells (35). There is some evidence that at least one of the complement components is such an enzyme (73). The antigen-antibody reaction may result in the lysis or breakdown of the antigen (1) (or antibody) releasing toxic products. Variations in this scheme have been a subject for speculation for many years (12, 98).

A more intimate relation of antigen or antibody with the cell may result in greater cell injury. Red cell lysis has been shown to occur with unrelated antigen-antibody reactions only if the antigen is absorbed on or chemically bound to the cell surface (34, 55, 101). Persistence of skin-sensitizing antibody at the site of injection (20) suggests an affinity between antibody and epidermal cell.

The most direct and probably most efficient form of cell injury is that in which the cell is an integral part of the antigen-antibody reaction. A correlation has been shown to exist between the skin-sensitizing capacity of a simple chemical and its ability to bind epidermal protein (31). This suggests that in this situation the antigen is a complex of the allergen and some tissue component. In cases of purpura due to sedormid and quinidine, the serum has been found to contain an antibody which reacts (fixes complement) only with the combination of the allergen and normal platelets (2). The failure of repeated attempts to demonstrate a reaction between allergen and skin-sensitizing antibody suggests that a third necessary component (the cell) may be missing from the reaction.

The above description of the various mechanisms by which cells may

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The above description of the various mechanisms by which cells may

receive allergic injury involves only the barest outline of these mechanisms. Some concept of the complexity of these reactions is provided by a study of the reactions between complement and sensitized red cells (75, 76, 81). The four components of complement (C_1, C_2, C_3, and C_4), and magnesium and calcium react with the sensitized cell (EA) according to the following scheme:

$$EA + C_1 + C_4 \xrightarrow{Ca} EAC_{14}$$

$$EAC_{14} + C_2 \xrightarrow{Mg} EAC_{142}$$

$$EAC_{142} + C_3 \xrightarrow{\Delta} E^* \rightarrow \text{hemolysis}$$

However, both EAC_{14} and EAC_{142} complexes undergo spontaneous inactivation in the absence of the components necessary for the succeeding step. In the presence of all components the alternative reactions are competitive.

Recent investigation reveals an equally complex role for antibody in the hemolytic process. In a system containing antibody, red cells and excess complement, the rate of hemolysis after a short lag remains constant over a long period of time as indicated by the exponential decline in the number of cells remaining unlysed (114). The fact that in most instances the rate of hemolysis varies with the square of the antibody concentration suggests that the simultaneous fixation of two molecules of antibody on adjoining sites on the red cell is required for complement fixation and hemolysis. Half of the red cells, each containing at least 75,000 antigen sites, are lysed in 30 minutes at 37°C. by less than 50 antibody molecules per cell. Under these conditions a single bimolecular pattern could be obtained on half of the cells within 30 minutes only if the antibody molecules moved at random from site to site with an average turnover time in the order of one minute. Since the avidity of the antibody for the cell determines turnover time, avidity is probably an important factor governing hemolytic efficiency. Too high an avidity would increase turnover time and reduce hemolytic efficiency. On the other hand antibody of too low avidity might not form a sufficiently stable bond with the red cell to permit the series of complement reactions necessary for hemolysis. Thus among antibodies of diverse avidity there is probably one which is optimum for the production of hemolysis.

The size of the antibody molecule also appears to play an important role in determining which of several possible reactions is predominant. With a large antibody molecule (estimated molecular weight, 900,000), the bimolecular reaction described above appears to be the most efficient. With a smaller antibody molecule, four or more molecules are required as suggested by the finding that the hemolytic rate in this case varies with the fourth power of the antibody concentration. Since chance combinations involving four molecules are much less frequent than those involving only two, these

findings explain the markedly greater hemolytic efficiency of the larger molecule (106).

The concept that antibodies differ in physico-chemical property and avidity for antigen is now well established. Despite this fact there has been relatively little investigation into the relation between these properties of antibody and the manifestations of antibody action. Most of the basic immunologic work of recent years has been done with the precipitating capacity of antibody as a frame of reference. Antibodies are held to be "complete" or "incomplete" depending on their ability to precipitate with antigen. However, precipitation is only one of many secondary reactions in which antibodies engage. Factors such as avidity, size, shape, and valence of the antibody molecule undoubtedly affect all of these secondary reactions, but not necessarily in the same way or to the same degree. Only by a direct study of the primary reaction between antigen and antibody can a basic understanding be obtained of the importance of these factors in a given secondary response.

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OBSTETRICS[1]

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Investigative work in both the clinical and preclinical aspects of obstetrics has increased tremendously within the past few decades, and the clinical applications of the results of this investigative work have produced an era which may be considered one of the most dramatic and significant in the history of this specialty. When one considers that as recently as 30 years ago the maternal mortality in this country was almost 10 per thousand and that now it is rapidly assuming a ratio of less than one per thousand, it is possible to realize what remarkable changes the practice of obstetrics has undergone in this country during this time. The gradual, but as yet by no means complete conquering of the three main maternal hazards in obstetrics—toxemia, hemorrhage, and infection—has permitted the obstetrician to peruse some of the less vital, but nevertheless crucial aspects of obstetrical care.

Investigative work during the past few years, therefore, in addition to being involved in the hazards listed above, has concerned itself with many of the less tangible and more psychologic aspects of maternal care, such as attempts to increase the comfort of the mother during the process of labor and parturition, the clinical care of the patient with various types of medical complications during pregnancy and delivery, and possibly most of all with the progress, development, and ultimate salvation of the infant during its growth from a blastocyst to a full-term, delivered, living baby.

Furthermore, the sociologic and economic aspects of obstetrics have received their share of thoughtful scrutiny during the past years; the very real and acute present-day problems of over-population, implications of therapeutic abortion and contraception, infertility in relation to obstetrics, and the responsibilities of obstetricians occupy an ever-increasing area of importance in our obstetric literature.

Population Control

Possibly in a review such as this, a brief summary of the obstetrician's point of view concerning his medical and social responsibilities in the field of over-population might serve as an introduction to his more clinical activities in the reduction of maternal and infant mortality. The startling and geometrically progressive increase in the world's population, with all its attendant problems and dangers, is becoming more and more apparent to us all and is interestingly described by Sir Charles Darwin (1). The obstetric implications and responsibilities of this increase are obvious. In a

[1] The survey of the literature pertaining to this review was completed in September, 1956.

study of what the potentialities of human reproduction might be if completely unrestrained by compulsive celibacy, custom, contraceptive techniques, or social pressures, Guttmacher (2) discusses two social groups, the Hutterites of the Middle West and the French-Canadian Catholics of Quebec, where reproductive capacity is unrestrained and, in fact, encouraged by religious and sociologic principles. In these groups he finds that the average reproductive potential of the reproductively uninhibited human couple is about nine offspring. The implications of such uninhibited reproduction as this are realized more than elsewhere in small island populations where the very real restrictions of space and food supply emphasize conditions which inevitably will occur throughout the world sooner or later if present population trends persist.

In a penetrating and "on the spot" survey of the problem of overpopulation in Japan, Pommerenke (3) describes a dramatic decline in death rate from 20.3 per thousand in 1900 to 8.9 per thousand in 1952 with, until 1950, a more or less stablilized birth rate. This increase in population will, if it continues at its present rate, reach the "explosive figure of 100 million by 1965." There are few ways to prevent such a population from starving on these islands where the agrarian potentialities are limited by acreage, the food from marine life by the ability of fishermen already wandering over the whole Pacific area to obtain it, and the financial potentialities of the country to import adequate food. Four proposals have been offered to solve this more and more untenable situation: (*a*) emigration, which the Japanese do not favor (nor apparently does any other civilized or uncivilized group); (*b*) continuation as the beneficiary of an international dole because their financial status does not provide them with the wherewithal to buy adequate food supplies, a status unacceptable to this or probably any other civilized country; (*c*) acceptance of a lower standard of living, which might have dangerous political repercussions; (*d*) restriction of the birth rate, which to the Japanese at least seems the least undesirable of these various choices.

The effective use of contraceptives not as yet being fully exploited, feticide to a degree unprecedented in modern civilization has therefore become legal in Japan. Abortions are "readily procurable on request and with little or no further investigation as to indication, and at a cost less in many instances than a New York City taxi fare to a hospital." The obstetric, moral, and sociologic implications of this attitude can easily be imagined, and one need only to refer further to Pommerenke's study of the problem to appreciate what can happen in this permissive environment. Certainly, regardless of any moral or religious implications, permissive abortion and feticide does not seem to be the medical answer to the ever more crucial problem of over-population.

The problem of casual use of "therapeutic abortion" is of course not restricted to Japan. In the Scandinavian countries, abortion has been legalized on almost any type of medical or psychiatric indication, and legal interruption of pregnancy in Sweden rose from 133 cases in 1935 to 5,503 in

1949 (4). Called "the doctor's dilemma" by Guttmacher (5), this obstetrician suggests an abortion committee for every hospital as a reasonable restrictive technique for prevention of the indiscriminate use of this technique of population control, and such an abortion board is, in fact, in existence in a large number of hospitals throughout the United States. To show actually how few therapeutic abortions can be carried out and a high grade of obstetrical competence still maintained, the Margaret Hague Hospital in Jersey City has permitted only eight therapeutic abortions in the last 140,000 deliveries and has still maintained in the last 56,000 deliveries a maternal mortality of less than one per thousand (6).

Thus it would appear that the obstetricians' concentration is not focused entirely upon techniques for decreasing maternal and infant morbidity and mortality, but is also involved to an ever-increasing degree in the vital problems of population control as being a legitimate area for research within the field of human reproduction. The search for a harmless, fool-proof, and uncomplicated contraceptive continues in various laboratories throughout the world, but until some type of simple oral medication can be found for this purpose it is doubtful if any of the present-day mechanical or chemical devices in use will have a very profound effect on world population (7).

Trophoblastic and Fetal Salvage

The concept of what constitutes an habitual or chronic aborter has not changed very much since the interesting mathematical deductions of Malpas in 1938 (8) and a subsequent confirmation of this mathematical definition by Eastman (9). Thus, the conventional idea that a woman who has had three or more spontaneous abortions is likely to have a common etiologic factor for all three classifies her as an habitual aborter, whereas a woman who has had one or two spontaneous abortions has about a 78 per cent chance that these abortions are attributable to adventitious, incidental factors which are not likely to repeat themselves. Randall *et al.* (10) state that repeated abortions occur in 1.4 to 4.7 per cent of pregnant women and that 10 to 20 per cent of all pregnancies terminate in abortion. Although Speert's series (11) presents a more optimistic result for the habitual aborter on the basis of the records of 17,490 obstetrical patients, there may be some question as to the accuracy of the findings in these patients because they were drawn from the patient's clinic charts which are known to be notoriously inaccurate so far as detailed information is concerned. Many patients, of course, are under the impression that they have aborted an indefinite number of times when actually it is possible that the patient was not necessarily pregnant at all. Furthermore, it is not unnatural for patients to have inaccurate recollections of their past obstetric histories so that deriving empiric data from histories of this sort may not be statistically permissible.

There have been continued efforts to treat habitual abortion by various types of hormonal therapy, the enthusiasm for estrogens having decreased somewhat over the past few years and given place to treatment with pro-

gesterone by various means or possibly with several different progestational hormones. Randall *et al.* (10) believe that progesterone deficiency may be detected by vaginal smear and suggest the administration of large amounts of progesterone intravenously to overcome the endogenous failure of progesterone production, whereas Wilson (12) suggests a hormonal program consisting of the oral administration of estrogen, progesterone-like ethinyl testosterone, and the intramuscular injection of chorionic gonadotrophin. Smith & Smith (13) still recommend stilbestrol therapy in threatened and habitual abortion and suggest its use very early in pregnancy beginning with 2.5 mg. daily at five weeks, increased gradually to 25 mg. in 15 weeks with a 5 mg. increase weekly thereafter until four weeks from term. They believe that the stilbestrol therapy technique stimulates increased placental secretion of progesterone and that therefore stilbestrol therapy will not maintain a defective trophoblast. Their technique of therapy has not met with universal acceptance, however, and Eastman (14), for instance, has stated that to date he has seen not a shred of evidence that stilbestrol therapy of any kind is beneficial in the treatment of habitual abortion. The treatment of repeated abortion with appropriate dietary additions in terms of concentrated vitamins of various sorts rather than with hormonal substitutes has been highly recommended by Javert (15), although he was among the first to recognize the possibilities of the stressful reactions of psychiatric, economic, and social problems as being possible etiologic factors in this difficulty (16). The psychiatric literature has been replete with considerations of psychiatric conflict as an abortion producer (17), but until recently there has been little coordinated effort on the part of obstetricians and psychiatrists to peruse this subject thoroughly from the point of view of both specialties. Recently, however, Mann (18) has made a study of habitual abortion in the Department of Obstetrics and Gynecology at the Cornell University Medical College and the New York Lying-In Hospital. Using psychiatric techniques of preconceptional psychiatric interviews, he has developed the proposition that abortion may be a physiologic somatic expression of psychiatric conflict and that appropriate psychotherapy may satisfactorily carry through many patients who would otherwise continue to abort. In fact, it is his belief that frequently the therapeutic value of various kinds of hormonal, vitamin, and other therapy is attributable to the fact that the physician administering these medications is carrying on an unconscious psychotherapeutic technique simply by expressing an interest in and concern for the patient.

Aside from spontaneous and chronic abortion as a source of trophoblastic failure, considerable interest has been expressed in recent years concerning the possibility that maternal virus diseases, especially rubella, in early pregnancy may produce either fetal death or very profound fetal injury resulting in blindness, deafness, or damage to other sense organs. Although Richards and co-workers (19) did not find a greater incidence of cardiovascular malformations in babies whose mothers had a high incidence of in-

fectious disease early in pregnancy, Greenhill (20) is of the opinion that fetal defects as a result of German measles occur in less than a fourth of infants whose mothers contract the disease during the first trimester. The defects include congenital cataract, heart disease, deafness, and central nervous system damage. Wesselhoeft (21) found evidence of large numbers of normal babies whose mothers had contracted rubella during the first three months of pregnancy, but he is nevertheless of the opinion that rubella early in pregnancy is an indication for therapeutic abortion. It is his impression that no other infectious disease is known to induce any such pattern of congenital deformity as rubella. The suggestion for therapeutic abortion must be decided, of course, according to the exigencies of the individual case. Religious principles, in many instances, do not permit abortion under any circumstances. Relative infertility, in some cases, possibly makes it worthwhile to take the chance that this will be an instance in which the fetus will not be affected. Last, but not least, the law in many states does not permit fetal indications for therapeutic abortions anyway. In the case of an individual who conceives easily, and if religious and legal considerations permit, it would probably be reassuring on a percentage basis therapeutically to abort a patient who had been proved to have rubella in the first trimester so that she could proceed with another pregnancy at a later date. This at least would increase her chances of having a normal baby.

Other genetic and intrauterine hazards to the welfare of the newborn occur in the presence of Rh incompatibilities and also possibly in incompatibilities in other blood groups. There have been no recent changes in the therapy of erythroblastosis other than an emphasis on exchange transfusion in the hope of preventing kernicterus or death from erythroblastosis. Allen & Diamond (22) state that there is still no agent of value in the prenatal treatment of erythroblastosis. Even with exchange transfusions, however, there is a high percentage of possibility of mortality or neurologic or psychic involvement in these offspring according to Kölbe (23).

The possibility that ABO blood group incompatibilities might produce fetal erythroblastosis has been the subject of considerable investigative work for a number of years (24, 25). Women of blood group O are thought to be susceptible to sensitization through antigen-antibody reactions to a fetus who has an A, AB, or B blood group. Turner (26) found that incompatible matings occurred in 22 per cent of all women attending the Queen Victoria Memorial Hospital in Melbourne. In 111 women with incompatible matings there were nine affected infants, four of which were first-born. Five of the nine affected infants were severely affected, and four mildly. Seven of the infants were of blood group A, mother of blood group O.

Having passed the genetic and environmental difficulties of the first trimester and the late abortion possibilities of the second, the growing fetus must pass through the possible dangers of prematurity before it reaches the next hurdle to viability, the hazards of delivery. According to Baird *et al.* (27) most of the deaths from prematurity are of unknown origin, and

it is only too true that the causes for early premature labor are as yet unexplained. Attempts to prevent premature labor by the use of relaxin (28) have been somewhat uncertain. To date bed rest and sedation seem to be the most satisfactory means of attempting fetal salvage from this cause.

Within the past year little has been written about the mechanical aspects of obstetrics although certainly mechanical trauma as a cause of fetal death must still be considered, it being responsible in at least one series for 20 per cent of the fetal deaths reported (27). The extensive use of anesthesia and analgesia, however, is thought to increase the amount of fetal anoxia at birth and thus require considerably greater resuscitation. Turner (29), in describing 79 maternal anesthetic deaths between 1946 and 1954 in Nashville, calls anesthesia "the fourth horseman of the obstetrical apocalypse," and Herron (30) discusses anesthesia as a maternal killer as well as being an anoxia producer in the infant. Attention to the increase of anoxia in maternal analgesia and anesthesia, as well as its potentialities for producing maternal deaths, has led to a consideration of prepared childbirth techniques whereby it is hoped that comfort throughout labor and delivery might be maintained with the use of only a minimal amount of obstetrical analgesia and anesthesia. The technique of the prepared childbirth program on the obstetric service of the School of Medicine of Yale University is extensively described by Buxton (31), and this technique is carried out in a somewhat similar fashion in many other institutions throughout the United States and Canada (32 to 35).

Evidence, however, of the gradual decrease in the number of term infants dying with traumatic brain hemorrhage has been presented by Anderson and his group at Johns Hopkins Hospital (36). In a review of the cases of brain hemorrhage in premature and term perinatal deaths on the obstetric service from 1937 to 1949, it was found that 9 per cent of the total deaths were attributable to intracranial hemorrhage. These were almost equally divided between premature and term infants. This group states

> Brain hemorrhage can be divided into two major categories, those initiated by anoxia (ventricular and subarachnoid hemorrhages), and those produced by mechanical trauma and associated with subdural hematomas or dural tears. Mechanical trauma plays a greater etiologic role in term infants, while anoxic brain hemorrhage is the principal lesion in premature infants.

In addition to the possibility of fetal mortality, this group stresses the permanent part which brain hemorrhage in the newborn may play in subsequent neurologic disturbances in the growing child, and with the improving techniques of forceps and other difficult deliveries, these writers plead for early recognition and management of maternal complications producing anoxia in which anesthesia plays a prominent role.

As might be expected, the recent enthusiasm for the use of tranquillizing drugs in various medical conditions has not gone unnoticed by the obstetrician in his management of labor and parturition. It is quite apparent that of

all times when tranquillity should be a desirable state of mind certainly the time of labor and delivery is high on the list, and the clinical evaluation of chlorpromazine in the management of labor has been studied in various clinics (37 to 40). Although some of the conclusions were quite contradictory (for instance, hypotension was minimal and required no therapy in one series but was considered potentially dangerous in its hypotensive effects in another), the general conclusion was that chlorpromazine potentiated the effects of various types of anesthesia and analgesia, and made the patients generally quieter, more co-operative, and more alert. One group felt, however, that it not only potentiated the good effects of the drugs used, but also occasionally accentuated the undesirable side effects, such as restlessness and excitement. It is interesting that there was no particular comment in any of these papers concerning the blocking effect of a tranquillizing drug in a patient's adrenergic response to stress which was so generally emphasized in several papers read at the last meeting of The Endocrine Society in June, 1956, but which are as yet unpublished (41, 42). Certainly labor and delivery is a stressful experience, and if the use of tranquillizers dulls the alertness of any physiologic response to stress, it is questionable whether these drugs should be used during the course of labor and delivery.

One of the changing trends in the mechanical management of labor has been the greatly increased usage of intravenous pitocin for the induction of elective labor or in connection with various obstetric complications. Williams & McMahon (43) found it to be an excellent adjunct to induce or aid labor, and in appropriately selected cases it certainly proved to be a satisfactory and innocuous obstetrical procedure. A number of papers concerning the intravenous use of pitocin during the past six or seven years have tended to strengthen the impression that when properly handled this drug is a definite obstetric aid (44 to 48). The present attitude toward the elective induction of labor is well expressed in an editorial in *Obstetrics and Gynecology* by Farrand (49), who states that he has induced about 700 patients during the past 20 years and therefore very reasonably feels qualified to comment not only on the process but the various different techniques used. The conclusion which he reaches, and this seems to express the general attitude toward this procedure, is that elective induction of labor when done under proper precautions and in proper circumstances presents a very satisfactory addition to the management and course of labor.

Although the problems of hemorrhage and toxemia in obstetrics were extensively commented on in last year's *Annual Review of Medicine* chapter on Obstetrics, it may be worthwhile to mention some of the continued interest which has been expressed in the obstetric literature during the past year concerning these complications.

In seeking to find a physiologic basis for the treatment of pre-eclampsia-eclampsia, de Alvarez (50) states that there must be some monitor system which during pregnancy maintains the homeostasis of normal electrolyte balance in spite of increases in total blood volume and total body fluids. A

derangement of this homeostasis in pre-eclampsia-eclampsia obviously occurs, but what the vascular and hemodynamic derangements are is as yet unknown, although certainly there is a marked reduction in the glomerular filtration rate, often to levels of 60 cc. per min., or even lower in some of the more severe degrees of this syndrome. Fluid and electrolyte imbalance must be controlled by electrolyte therapy based on known electrolyte excretion, with replacement of electrolytes only in accordance with the anticipated output and the status of serum electrolytes. Daily weight change offers the most exact index of insensible fluid loss, and fluid administration must be based upon accurate and fundamental knowledge of water balance. In commenting on the vaso-depressor drugs, Chesley (51) states that in general, the ganglionic blocking agents and the adrenolytic drugs have little effect, and he prefers those which act directly or indirectly upon the arteriolar segment. The veratrum preparations and 1-hydrazinophthalazine (Apresoline) appeared to have this action, the latter drug increasing cardiac output, renal blood flow, cerebral blood flow and oxygen consumption. The use of magnesium sulphate in the prevention of convulsions he considers to be more satisfactory than any other technique, and suggests an initial intramuscular injection of 10 gm. (20 cc. of a 50 per cent solution) followed by 5 gm. doses at intervals of 6 hr. The most satisfactory technique of treatment of the severe pre-eclamptic, therefore, is by the use of magnesium sulphate and vasodepressor drugs, with a minimum use of barbiturates and other sedatives.

In a review of a large number of toxemic women for whom he was able to find records of prepregnancy blood pressures, Tillman (52) concluded that in the vast majority of cases an unrecognized previous hypertensive state is responsible for the appearance of hypertension during and following toxemia of pregnancy. He found that the woman who exhibited hypertension solely in pregnancy was hypertensive prior to pregnancy, and the patient who developed a pre-eclamptic syndrome in pregnancy may have been either normotensive or hypertensive prior to pregnancy, and that her postpartum blood pressure will reflect her prepregnancy state. Toxemia of pregnancy was not found to increase hypertension permanently.

Coagulation defects and acute fibrinogen deficiency continue to be an increasingly recognized etiologic factor in some of the acute hemorrhagic crises which occur occasionally in obstetrics. A review of the general mechanisms of production of acute fibrinogen deficiencies by Schneider (53) suggests the idea that defibrination results from fibrination followed by fibrinolysis. An acute hemorrhagic diathesis in a situation where defibrinated blood is continuing to circulate does not usually result in actual bleeding unless there is a laceration or surgical incision from which the bleeding may occur, such as cervical or perineal lacerations in vaginal deliveries or abdominal incisions in Cesarean section.

Reid and co-workers (54) emphasize the defective coagulability of the blood in certain obstetric complications, especially in the more severe forms

of premature separation and after fetal death *in utero*. Obstetric patients are able, generally, to withstand moderate losses of blood without shock; consequently when shock does appear it may mean that the patient is nearly exsanguinated. Detection and treatment of the syndrome of hypo-fibrinogenemia may be of crucial importance in such patients. If fetal death *in utero* occurs the mother should have a weekly clotting examination test. The clotting mechanism should be corrected before any obstetric procedure is contemplated, and this is readily accomplished by transfusion and fibrinogen. These writers do not state how long they feel it permissible to allow a woman to continue with a fetal death *in utero* before delivery, but they imply that such a patient as this may be left alone for a number of weeks if she is carefully watched by weekly clot observations and possibly plasma fibrinogen concentration levels. She should be cautioned to report immediately any bleeding from the reproductive or gastrointestinal tract, or into the subcutaneous tissues.

The treatment of afibrinogenemic crises has been greatly benefited in many states by the careful state-wide distribution of fibrinogen and the establishment of a distribution technique whereby, with the assistance of state police or ambulance service, the material may be delivered to any obstetric service in the state within a matter of less than an hour.

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DISEASES OF THE NERVOUS SYSTEM[1,2]

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In this review, recent advances have been summarized with an emphasis on some of the more common disorders of the nervous system. Some unusual clinical entities are included where new information has been acquired as to the pathophysiology of diseases previously considered as "degenerative" in nature or as of unknown etiology. The increasing interest in the biochemistry of the nervous system is evidenced by the appearance of several monographs, (1 to 3) and a new journal (4) devoted to this subject. It is likely that research in this area will hasten the disappearance of "degenerative" and "idiopathic" from the neurological vocabulary.

CEREBROVASCULAR DISEASE

Intracranial aneurysm.—Walker (5) has analyzed 285 cases of intracranial aneurysm and vascular malformation with regard to symptoms, localizing signs and clinical course. Accurate localization of the lesion is generally dependent upon angiography, but in many cases the clinical findings alone may be sufficiently characteristic to permit localization. The signs of aneurysm of the infraclinoid portion of the carotid artery, prior to rupture, were those of involvement of the nerves traversing the cavernous sinus. Most commonly there was a third nerve palsy, and pain and sensory loss in the distribution of the first and second divisions of the trigeminal nerve. The fourth and sixth nerves were also involved in some cases. Less commonly, ipsilateral exophthalmos was noted. These aneurysms generally did not rupture into the subarachnoid space but rather into the cavernous sinus. In some cases, such arteriovenous fistulae presented with a bruit, audible to the patient and physician, antedating the development of a pulsating exophthalmos. In 10 per cent, the latter was bilateral; rarely, only the eye contralateral to the fistula was involved. Visual loss was also noted due to involvement of the optic nerve by the associated papilledema. Aneurysms of the supraclinoid portion of the internal carotid artery ruptured into the subarachnoid space and also frequently involved the third nerve. Aneurysms of the basilar and vertebral arteries were noted in 17 cases in this series. Five of these were asymptomatic and found incidentally at autopsy. Seven presented no localizing signs prior to rupture. In the remainder there was variable involvement of the third to the eighth cranial nerves. In a few cases there were symptoms suggestive of intermittent com-

[1] The survey of literature pertaining to this review was completed in July, 1956.

[2] The following abbreviation has been used in this review: BAL (2,3-dimercaptopropanol).

pression of the brain stem or insufficiency of the basilar artery. There were 84 cases of vascular malformation in this series which presented most commonly as a convulsive disorder. Both Jacksonian and generalized convulsions were noted. Subarachnoid hemorrhage and a neurological deficit, typically a hemiparesis, were also common symptoms. A bruit was noted in only five cases. Ninety per cent of the patients had symptoms before the age of 40 years.

Treatment of subarachnoid hemorrhage.—The role of carotid artery ligation in the neck in the management of subarachnoid hemorrhage secondary to ruptured aneurysm has not been clearly established. Roe *et al.* (6) have reviewed the literature from 1944 to 1955 and point out that the average mortality was 21 per cent in direct intracranial attack on aneurysms, while the mortality after ligation of the carotid artery in the neck was 8 per cent. In view of the many differences between both patient populations no specific conclusions could be made, although the authors did state that both operations have a place in therapy.

Magladery (7) has reviewed the problem of management of patients with subarachnoid hemorrhage by considering the hospital course of 235 unselected patients with subarachnoid hemorrhage considered secondary to ruptured aneurysm. Of these, 37 were treated with carotid ligation in the neck or by direct intracranial attack. The mortality rate in the total series was over 50 per cent. It was particularly high in patients over the age of 50, in the presence of hypertension, and in patients who were comatose at the time of admission. Most deaths occurred during the first 24 hr. after admission. In patients who survived seven days, the mortality with conservative therapy was less than 20 per cent, and after 21 days the mortality was less than 12 per cent. The results of surgical therapy did not differ greatly. Magladery (7) points out that there are insufficient data to support the view that either carotid ligation or direct intracranial attack offer any better result than conservative management.

Whereas the value of surgical therapy of congenital aneurysm is still in dispute, it would appear that direct intracranial attack for clipping or ligation of the aneurysmal neck, when possible, is a more rational procedure than ligation of the carotid artery in the neck. The introduction of newer neurosurgical techniques, in particular the use of hypothermia during surgery, has been reported to improve the results obtained with the direct intracranial attack (8).

Carotid and basilar artery insufficiency.—The syndrome of intermittent insufficiency and occlusion of the carotid artery has been recognized for many years. The high incidence of carotid artery occlusion has been emphasized by the report of 28 cases of complete occlusion and 13 cases of severe narrowing of the lumen occurring in 432 consecutive routine autopsies in a general hospital (9). Occlusion may be unaccompanied by demonstrable changes in the brain, or may be associated with unilateral or bilateral softenings. In 13 cases there was an organic dementia suggesting that carotid artery

insufficiency may be of importance in the pathogenesis of the senile dementias. The relatively infrequent post-mortem examination of the carotid arteries in the neck and skull has probably concealed the high incidence of occlusion in the past.

In cases of basilar artery thrombosis, there may be intermittent symptoms and signs prior to a fatal occlusion. The diagnosis of basilar artery insufficiency is suggested by intermittent episodes of hemiparesis associated with diplopia, vertigo, dysarthria, dysphagia and other signs of brain stem involvement. The variable course may be attributed to varying degrees of ischemia or infarction in the regions supplied by the basilar artery (10).

Meyer *et al.* (11) have studied 36 patients with recurrent symptoms attributed to insufficiency of the internal carotid and basilar arteries. These patients were particularly sensitive to the reduction in blood pressure produced by postural change on the tilt table. Electroencephalographic changes induced in this manner are believed secondary to transient focal cerebral ischemia. The authors suggest that recurrent, intermittent neurological symptoms in patients with cerebrovascular disease may be attributable to a failure of cerebral collateral circulation in a compromised vascular territory rather than caused by a varying degree of "vasospasm" in the affected artery. A fall in systolic blood pressure is considered a frequent cause of failure or impairment of the collateral supply. Insufficiency of the internal carotid or basilar arteries may give rise to generalized disturbances associated with syncope, mental confusion, episodic dementia and seizures, as well as focal signs. In the therapy of such syndromes maintenance of blood pressure is of primary importance. In view of the hazards of postural hypotension, the authors state that chlorpromazine, rauwolfia alkaloids and hypotensive drugs are generally contraindicated since they tend to increase postural hypotension. The use of tight abdominal binders and elastic stockings may be of value. Ephedrine and atropine may minimize the carotid sinus depressor mechanism which is hyperactive in many of these patients and thus prevent postural hypotension. The use of anticoagulant therapy may also be of value.

Fazekas *et al.* (12) have studied the cerebral complications of hypotension induced by the administration of hexamethonium and trimethaphan (Arfonad). This may result in alterations in consciousness, convulsions, and focal neurological signs. Patients with hypertension and cerebrovascular disease are more susceptible to these complications of hypotension than are normal controls.

Anticoagulation.—There have been several favorable reports of anticoagulation therapy in the management of cerebrovascular disease. Millikan *et al.* (13) have reported five patients with intermittent attacks of basilar artery insufficiency which stopped following adequate anticoagulant medication. They have also reported a mortality rate of 12 per cent in 25 patients with basilar artery thrombosis treated with anticoagulation. In a control group of 23 untreated patients the mortality rate was 43 per cent. Anticoagulant therapy has also been recommended in the treatment of inter-

mittent insufficiency of the internal carotid artery (14). Wright & McDevitt (15) have discussed the use of anticoagulants in the management of thromboembolic phenomena involving various structures including the nervous system, secondary to myocardial infarction, auricular fibrillation, and rheumatic endocarditis. Whether anticoagulation has a place in the management of the common primary thromboses of the cerebral arteries is as yet undetermined. There is a potential hazard of anticoagulation therapy in patients with hemorrhagic infarction or intracerebral hemorrhage which should caution against the indiscriminate use of anticoagulants in patients with cerebrovascular disease.

EPILEPSY

Medical therapy of epilepsy.—Yahr & Merritt (16) have reviewed the current status of the drug therapy of epileptic seizures. They point out that seizures can be completely controlled in 50 per cent of the patients and greatly reduced in another 35 per cent. They have outlined the common pitfalls in the failure to obtain maximal control. Improper classification of the seizure type is a common error, particularly the confusion of minor grand mal and psychomotor seizures with petit mal attacks. This frequently results in the failure to use the proper drug. Trimethadione (Tridione), the drug of choice in the treatment of petit mal, is entirely ineffective against major seizures. The hydantoin and barbiturate derivatives, most effective against major attacks, have little or no beneficial effect on petit mal seizures. The failure to administer an adequate dosage is the major cause for failure in the control of convulsive seizures. Following selection of the proper drug or combination of drugs, it must be remembered that there is no fixed dosage of the anticonvulsants. The medication should be started with what is assumed to be a minimum dose and gradually increased until the seizures are controlled or toxic reactions to the drug develop. If the latter occur without seizure control, the drug is not discontinued (unless toxic symptoms are of a dangerous nature), but doses are reduced to a non-toxic level and a second drug is given following the same principle of increasing dosage. The combined administration of two or more drugs in this manner may be far more effective than any one drug administered alone. Frequent shifting of drugs, without a trial with the maximal dosage possible, should be avoided. The use of new anticonvulsants should usually be reserved for patients resistant to therapy with adequate dosages of well established drugs. Anticonvulsant medication should not be discontinued after a relatively short seizure-free period. In general, treatment should be continued for at least two to three years after the last seizure. When medication is to be discontinued, it must be done gradually over a period of a year or so depending on the original dosage level. Failure to recognize a progressive neurological disease is another reason for failure in treatment. Seizures may be the initial symptom and may precede other symptoms of tumor or other diseases of the nervous system by many years. Detailed neurological examination and laboratory

studies should be carried out when anticonvulsant medication is begun, and periodic re-examinations are necessary. The onset of symptoms of a progressive disease of the nervous system may be mistaken for toxic reactions to drugs in patients under treatment for seizures.

Surgical therapy of epilepsy.—The indications for surgery in the treatment of epilepsy are generally limited to patients whose seizures cannot be controlled with medication and who have clinical and electroencephalographic evidence of a focal cerebral lesion which may be excised. The difficulty in evaluating the results of surgical treatment is due, in part, to the very heterogeneous nature of the lesions in such patients, and to differences in surgical technique. It is also likely that all clinics are not in agreement as to what constitutes failure in drug therapy.

Penfield & Paine (17) have reviewed the results of surgical therapy for focal epileptic seizures in 234 patients in whom medical therapy was considered unsuccessful. The seizures were classified as secondary to the following: birth or post-natal trauma in 70 per cent of the patients; local suppuration in 5 per cent; cortical thrombophlebitis in 4 per cent; angioma in 3 per cent; hemangioma calcificans in 2 per cent, miscellaneous lesions and lesions of uncertain etiology in 8 per cent each. In all patients phenobarbital was used routinely as a postoperative anticonvulsant. Patients requiring additional anticonvulsant medication were classified as failures. There were 268 craniotomies in 234 patients with negative explorations in 15 and an operative mortality of 1.5 per cent. In the 203 patients followed postoperatively for at least three and one half years, 28 per cent were seizure free, 17 per cent had fewer than three seizures, 20 per cent were considered as improved, and 35 per cent were considered failures. In 15 of 159 patients with a normal neurological examination preoperatively, a motor or sensory deficit developed postoperatively. Of the 234 patients, 28 were classified as having temporal lobe seizures. Partial temporal lobectomy was successful in about half of the cases. Postoperative complications included transient or permanent visual field defect, aphasia, and memory impairment.

In selected patients with uncontrolled convulsive seizures associated with infantile hemiplegia, cerebral hemispherectomy has proved of value. Removal of the abnormal hemisphere has resulted in complete control of seizures in eight of nine cases reported by French *et al.* (18). The pre-existing neurological deficit was not aggravated, and in one case there was definite improvement. There was no evidence of an increased intellectual deficit, and in some there was a definite improvement in their personality adjustment, probably related to the control of seizures. Ransohoff & Carter (19) have also reported that hemispherectomy is the treatment of choice in patients with uncontrolled seizures associated with an infantile hemiplegia. They also noted no change in the motor deficit postoperatively. The improvement in behavior and the control of seizures was also associated with a marked improvement in the postoperative electroencephalogram.

Temporal lobe and psychomotor epilepsy.—The association of lesions in the

temporal lobe and psychomotor seizures has been frequently reported. Penfield (20) has summarized his observations of the effects of electrical stimulation of the temporal lobe in epileptic patients at operation. Stimulation of the lateral and superior surfaces of the temporal lobe at times produced psychic responses suggesting that the patient was reliving an earlier experience in great detail. At such times, the patient remained conscious while re-experiencing visual, auditory, and even somatic sensations. Such phenomena could only be activated in a cortex apparently conditioned by years of electrical discharge from a neighboring epileptogenic focus. Penfield considers this a stimulatory replying of a portion of the stream of consciousness rather than as a memory, as ordinarily defined, which implies a voluntary act of recollection.

Penfield (20) classifies seizures arising from epileptogenic foci in the temporal lobe into three groups: (*a*) experiential seizures, (*b*) interpretive seizures, (*c*) automatisms (psychomotor seizures). The experiential attack is an hallucination of past experience. The patient may refer to it as a flash back or dream. It resembles the psychic phenomena which may be evoked by electrical stimulation of the cortex, as described above. Interpretive seizures are composed of an illusion in regard to present experience, such as a feeling of unfamiliarity or familiarity (*dĕjà vu* phenomena). The automatisms are marked by periods of automatic behavior. In the first two types of attacks, the epileptic discharge at operation occurs in the lateral or superior surface of the temporal lobe. In patients with automatisms the epileptic discharge most commonly appears to arise in the vicinity of the amygdaloid nucleus.

Bailey (21) has summarized his experiences with surgical treatment of 92 patients with psychomotor epilepsy associated with an electroencephalographic focus in the anterior temporal region. Extirpation of the anterior temporal lobe was followed by freedom from attacks in 64 per cent, either without anticonvulsant medication or with doses which were ineffective preoperatively. Only 23 per cent of patients with bilateral foci were improved by operation. About 45 per cent of patients were relieved of psychotic manifestations. In three cases, transient hypersexual behavior was noted, reminiscent of the behavior change produced in monkeys by a similar operation. In 24 per cent no improvement in the seizures resulted. In most patients no gross pathology was noted; in some there was evidence of old trauma; and in three patients unsuspected neoplasms were found.

The relationship of minor pathological changes in the temporal lobe to epilepsy is uncertain. Crome (22) has evaluated the pathological change in the temporal lobes of 29 non-epileptic patients, 21 mental defective patients without epilepsy, and 61 mental defective children with epilepsy. In all three groups, abnormalities were noted, including meningeal fibrosis, gliosis, cortical atrophy, and cellular degeneration. Sclerosis of Ammon's horn was common in the mental defectives with or without seizures. Crome cautions that the presence of such lesions in the temporal lobe does not prove their responsibility for epilepsy.

Post-traumatic epilepsy.—Walker (23) has studied the natural history of

post-traumatic epilepsy by reviewing the course of 246 men ten years after head injury. The patients were a heterogeneous group with regard to the original injury, frequency of seizures, neurological deficit, and therapy. However, there was a definite tendency for the seizures to decrease after two or three years. The seizures ceased after five years in 45 per cent of cases.

METABOLIC DISORDERS OF THE NERVOUS SYSTEM

Hepatolenticular Degeneration

There has been considerable interest in the metabolic alterations associated with hepatolenticular degeneration or Wilson's disease. There is a major derangement of copper metabolism, as evidenced by the increased copper content of brain and liver (24). This is associated with a total serum copper which is usually reduced because of a deficiency of the copper containing serum globulin, ceruloplasmin (25). The urinary excretion of copper is also characteristically increased (25). In addition there is a disturbance of amino acid metabolism with increased urinary excretion of amino acids (26) and specific oligopeptides (27) associated with a normal serum alpha amino nitrogen level.

The major portion of the total serum copper is normally bound to the alpha-2 globulin, ceruloplasmin. This does not react directly with sodium diethyl-dithiocarbamate and is considered as the indirect reacting fraction (28). A smaller fraction (0 to 17 per cent), probably loosely bound to albumin, which does react with this reagent, has been termed the direct reacting serum copper. In Wilson's disease, the increase in the direct reacting fraction has been considered as probably secondary to the deficiency of copper-binding globulin, ceruloplasmin. Cartwright *et al.* (28) studied the spinal fluid in six patients with Wilson's disease and found the concentration of copper to be three times that in a control group. In the latter, half the copper was of the direct reacting type but in the patients all the copper was of the direct reacting type. It is suggested that the greater diffusibility of the direct reacting copper (non-ceruloplasmin copper), as evidenced by these spinal fluid data, as well as by Scheinberg's observations on transplacental copper exchange (25), facilitates the deposition of copper in brain, liver, and other tissues.

Scheinberg (25) considers a plasma ceruloplasmin level below 15 mg. per cent a sufficient criterion for the diagnosis of Wilson's disease in a patient who is not newly born or suffering from nephrosis when such low levels may also occur.

Cartwright *et al.* (28) also performed copper balance studies in patients with Wilson's disease, three normal individuals, and two patients with active rheumatoid arthritis. In the normals, intake and output were essentially equal, but in the patients with Wilson's disease and with rheumatoid arthritis there was a positive copper balance. In an autopsied case of Wilson's disease the concentration of copper was increased in all tissues except the heart but was most marked in the liver and brain stem.

Bearn & Kunkel (29) have reported that the oral administration of radio-

active copper to the normal subject and to patients with Laennec's cirrhosis is followed by immediate uptake of copper by the serum albumin. Within a few hours the tracer copper shifts to the ceruloplasmin fraction. In patients with Wilson's disease, however, the radioactive copper was not transferred to the ceruloplasmin fraction but largely remained with the serum albumin. They suggest that the albumin fraction is normally concerned with the transport of copper to various tissue proteins and to ceruloplasmin and that the impaired transfer in patients with Wilson's disease is due to the deficiency of ceruloplasmin.

Matthews (30) has administered radioactive copper orally to two patients with Wilson's disease and found that the plasma levels of the tracer were slightly higher than in controls. He also noted that the urinary excretion of radioactive copper was higher in the patients than in the controls, but that the fecal excretion was reduced in the patients as compared to the control group.

The nature of the amino-aciduria in Wilson's disease has been further explored by Stein *et al.* (31) using a chromatographic method which permits the more accurate identification and measurement of amino acids in biological fluids. The plasma amino acids were not qualitatively nor quantitatively different from the normal. There were abnormalities in the urinary excretion of amino acids in five of six patients and one had an almost normal excretion pattern. The highest levels of urinary excretion were noted for threonine and cystine (20 times normal). Serine, glycine, asparagine, valine, tyrosine, and lysine, and possibly glutamine, were excreted in five to ten times normal amounts, and histidine, ornithine and phenylalanine in two to four times normal quantities. Two amino acids, proline and citrulline, not normally found in urine, appeared in considerable quantities in some cases. There was a reduced excretion of taurine and the methyl histidines as compared to the normal. In patients with Wilson's disease the quantity of amino acids excreted in conjugate linkages was about double the normal. The amount of protein in the diet was found to have little effect in normal individuals on the patterns of urinary excretion of amino acids. In the patients with Wilson's disease, however, variation in the dietary intake of proteins resulted in marked differences in the level and pattern of the urinary amino acid excretion. These investigators agree with the previous conclusion that the amino-aciduria in Wilson's disease is the result of a renal lesion. While some of their data are suggestive of a lowered renal threshold for amino acids in this disease, they point out that the reduced excretion of taurine and the methyl histidines cannot be readily explained in this manner.

There is evidence of a correlation betwen the defects in copper and amino-acid metabolism in Wilson's disease (28). The administration of cortisone and increased protein intake induces a prompt and parallel increase in urinary copper and amino acid excretion (32). Similarly the administration of casein hydrolysate (28), glycine, and alanine (33) was noted to be associated with increased urinary excretion of copper in patients with Wilson's disease. However, in a study of a single patient with marked amino-aciduria and

increased urinary copper excretion, Uzman (34) reported that the daily output of copper had no direct relation to the amino-aciduria. He has stated that the urinary copper in Wilson's disease is present mainly as a complex with urinary peptides having dicarboxylic amino acids as terminal residue.

In Wilson's disease, approximately 58 per cent of the total urinary copper is dialyzable. Although the total urinary copper excreted is increased by the administration of casein hydrolysate, the percentage of dialyzable urinary copper is essentially unchanged. However, the administration of BAL or intravenous calcium edathamil (EDTA, Versene) results in an increased urinary copper excretion which is 80 per cent dialyzable which suggests that these agents effect the increased excretion by different mechanisms. The use of orally administered edathamil does not appreciably increase urinary copper excretion (28).

At present there is some disagreement as to whether the primary defect in Wilson's disease is a disturbance of copper metabolism or amino acid metabolism. Scheinberg & Gitlin (35) have proposed that the inherited defect is a deficiency of ceruloplasmin. Some workers (32) have emphasized the increased copper absorption associated with a deficiency of the binding protein ceruloplasmin which results in an increased readily diffusible copper fraction. This in turn ultimately produces deposits of copper in the cornea, brain, liver, and other tissues. Thus, the amino-aciduria and peptiduria have been considered secondary to functional impairment of the kidney due to copper accumulation (28). At present it is uncertain as to whether the hypoceruloplasminemia is a result of decreased rate of synthesis or increased rate of destruction of this protein. A conflicting hypothesis considers the disorder to be a primary defect in amino acid metabolism, leading to the accumulation of abnormal peptide residues in cells which bind copper (34). Such copper binding oligopeptides are released into the blood and the amino-aciduria is considered to result from competition between these peptides and the amino acids by the renal tubules, leading to the incomplete absorption of the oligopeptides and marked amino-aciduria. This alternate hypothesis is contradicted by the report of patients with the disturbance in copper metabolism characteristic of Wilson's disease, but without an abnormal increase in amino acid excretion (25).

Cartwright *et al.* (28) have made some definite therapeutic suggestions as a result of their observations of the positive copper balance characteristic of Wilson's disease. Their patients were in positive copper balance as high as 0.5 to 2.5 mg. of copper per day. The administration of chelating agents mobilized about 0.5 to 1.0 mg. per day, at times insufficient to establish a negative copper balance, and effective only as long as the agent was supplied. In view of these findings, they were surprised that any of the patients were benefited. However, they have recommended long term therapy as follows: (*a*) a high protein diet to increase urinary copper excretion associated with the concomitant amino-aciduria; (b) 20 mg. of potassium disulfide with each meal to decrease the absorption of copper; (c) five day courses of BAL (2.5 mg. per kg., twice daily) or casein hydrolysate (one l. of 5 per cent solu-

tion per day), to be given every ten days until maximal improvement is noted. They feel this regimen should be maintained continuously, if possible. Repeated injections of BAL are painful and may be associated with undesirable side reactions.

Walshe (36) has reported that penicillamine, (β,β-dimethyl-cysteine) is effective in promoting copper excretion in patients with Wilson's disease. The urinary excretion of penicillamine in the reduced (SH) state has been noted in patients following the administration of penicillin. In view of this observation Walshe hypothesized that penicillamine might remain in the reduced form if administered orally, and that the thio group might be active in binding copper and would increase urinary copper excretion. Following the oral administration of penicillamine to two patients with Wilson's disease, he found the increase in copper excretion to be as great as that following BAL therapy. No toxic reactions were observed in short term experiments.

Liver Function and Neurological Disorders

There is additional evidence of the dependence of the nervous system upon the normally functioning liver. Geiger *et al.* (37) have shown that the isolated perfused brain requires the presence of the liver in the perfusion system, or of substances present in fresh liver extract, for the uptake of glucose and oxygen and for normal electrical activity. The nature of such "activators" in liver has not as yet been determined. Sherlock *et al.* (38) have reviewed the neurological complications of liver disease in 18 patients. They emphasize episodic clouding of consciousness and coma (insidious or abrupt in onset), ataxia, flapping tremors of the outstretched hands, hyperreflexia, reversal of sleep patterns, muscular twitching, grasping and sucking reflexes, and disorders of speech and vision. Neurological signs in some patients lasted as long as three years; more frequently they lasted about one week, followed by either recovery or death. It is suggested that the damaged liver is unable to metabolize nitrogenous substances of portal venous origin, and therefore such substances are able to reach the systemic circulation. Major portal-systemic collateral channels also enhance the concentration of these substances in the systemic circulation. The neurological syndrome in such cases has been termed "portal-systemic encephalopathy."

The importance of ammonia metabolism in the pathogenesis of hepatic coma has been re-emphasized. McDermott & Adams (39) studied a patient with a portacaval anastomosis, in whom neurological signs and electroencephalographic changes suggesting hepatic coma were induced by the administration of ammonium containing compounds. The signs were reversible when these compounds were stopped. The neurological changes were correlated with a high plasma ammonia level. Others have shown that the administration of ammonium releasing cation exchange resins as well as nitrogenous foodstuffs to cirrhotic patients resulted in signs of hepatic coma associated with an increased plasma ammonia level (40). However, while there is generally an increase in blood ammonia with the appearance

of neurological signs, correlations of fluctuations of the two are subject to great variation, and the blood ammonia level is a poor prognostic guide during hepatic failure (41). It appears likely that other metabolic products not detoxified by a damaged liver, as well as bacteremia, electrolyte disorders and other neurological disorders associated with alcoholism, contribute to the clinical picture seen in liver failure. The importance of a high protein diet in compensated liver disease has been emphasized, but in the presence of liver failure there is a potential danger in giving a high protein diet and ammonium containing compounds. The use of intravenous glutamic acid has been recommended in the management of liver failure, but its value is still uncertain in view of conflicting reports as to the results of such therapy (42).

Porter & Adams (43) have analyzed the brain and liver for total copper in 11 cases of fatal hepatic failure not associated with Wilson's disease, to investigate the possibility that there might be a disorder of copper metabolism in hepatic encephalopathy. Most of the patients had Laennec's cirrhosis. There was no evidence of a consistent increase in the total copper of brain or liver in any of the cases studied.

Galactosemia and Phenylpyruvic Oligophrenia

In these diseases there is an inborn metabolic defect which prevents normal utilization of a usual dietary component, suggestive of the kind of abnormality found in Wilson's disease.

Congenital galactosemia is a rare disorder of carbohydrate metabolism in children, associated with mental and physical retardation, cataracts, hepatosplenomegaly and ascites. The disease is characterized by an elevated blood galactose and galactosuria. There may also be amino-aciduria, particularly after the administration of galactose to the patient. Clinical improvement may occur if the child is placed on a galactose free diet, and the mental retardation may be prevented if this is done early in the course of the disease. Schwartz *et al.* (44) have shown that the administration of galactose to infants with the disease is followed by marked accumulation of galactose-1-phosphate in the erythrocytes. Isselbacher *et al.* (45) have recently reported that infants with galactosemia have a deficiency of a specific enzyme, phosphogalactose-uridyl-transferase, necessary for the normal conversion of galactose to glucose-1-phosphate. The relationship between this biochemical defect and the pathological findings in this disease is as yet undetermined.

Phenylpyruvic oligophrenia is a disease of children characterized by mental deterioration, convulsions, dermatitis, fair hair, and a musty odor. The metabolism of ingested phenylalanine is impaired and it is excreted in the urine with its derivatives, phenylpyruvic and phenyllactic acids. A low phenylalanine diet results in a rapid fall in the blood level of phenylalanine and a fall in the urinary excretion of phenylalanine and its derivatives (46, 47). Bickel *et al.* (46) have reported that the hair darkened, the skin lesions improved and the musty odor disappeared after administration of this diet.

Some improvement in the mental and motor performance of the children was also described. Meister *et al.* (48) have reported that following the oral administration of glutamine there was a marked reduction in urinary excretion of phenylpyruvic and phenyllactic acids. There were no changes in the blood levels or urinary excretion of phenylalanine. The possible value of glutamine in the therapy of the disorder has not as yet been determined.

MYASTHENIA GRAVIS

The pathophysiology of myasthenia gravis is obscure but it is generally accepted that there is a failure of neuromuscular transmission in this disease. In brief, present concepts emphasize the occurrence of the following successive events in normal transmission of the nerve impulse across the neuromuscular junction: arrival of the nerve impulse at the junction is associated with the release of bound acetylcholine which combines with specialized receptor sites on the end plate membrane surface; this is associated with a decrease in the transmembrane potential (depolarization) which probably is a function of redistribution of sodium and potassium ions across the membrane; the muscle action potential is evoked and muscle contraction follows; the acetylcholine is hydrolyzed by cholinesterase to form acetate and choline; the resting membrane potential is re-established; choline and acetate are resynthesized by the enzyme cholineacetylase to reform bound acetylcholine; and the end plate and relaxed muscle fibre are then ready for repetition of the cycle (49).

Neuromuscular transmission may be impaired as result of a deficiency or an excess of acetylcholine. Drugs such as an anticholinesterase permitting the local accumulation of acetylcholine, result in abnormally prolonged depolarization of the end plate. The depolarized end plate prevents neuromuscular transmission. Compounds such as succinylcholine, decamethonium and neostigmine (Prostigmin) in high dosages, are considered as "depolarizing neuromuscular blocking agents" whereas drugs such as d-tubocurarine which block neuromuscular transmission by competing with normally released acetylcholine for a common receptor site on the end plate are considered as "competitive neuromuscular blocking agents" (50).

Recent experiments based on these concepts have led to a revision of the previous hypothesis that there is decreased sensitivity of the end plate to acetylcholine in myasthenia gravis. Grob *et al.* (51) have studied the effects of injection of acetylcholine, acetate, choline and other compounds on neuromuscular transmission in myasthenic patients and normal subjects. Their findings suggest that neuromuscular transmission is normal in myasthenia through the stage of the production of choline which follows the hydrolysis of acetylcholine. However, the choline produces a competitive type of block in the end plate membrane which inhibits the depolarizing action of acetylcholine released by subsequent nerve impulses, resulting in a failure of muscular contraction. In normal subjects, choline produces a predominantly depolarizing block unlike the competitive block. This striking difference in the type of block produced by choline in the normal

and myasthenic state may be explained by either an abnormal response of the end plate in myasthenia, or by the formation of an abnormal product of choline in myasthenia which acts as a competitive blocking agent.

Churchill-Davidson & Richardson (52) have observed that decamethonium produces a depolarizing type of block in normal subjects unlike the competitive type of block which results in myasthenic patients. They have concluded that these findings are not compatible with the hypothesis that there is a circulating or locally produced curare-like substance in myasthenia. The major support for the latter hypothesis is derived from the occurrence of transient neonatal myasthenia in the offspring of mothers with myasthenia gravis (53).

The management of patients with myasthenia gravis has depended largely on the administration of neostigmine. This anticholinesterase has major disadvantages including a relatively short period of effectiveness, troublesome side effects, particularly gastrointestinal distress, and most important, failure of the drug to reverse myasthenic symptoms particularly in severe forms of the disease. A number of other anticholinesterases, including tetraethyl pyrophosphate, octamethyl pyrophosphoramide, and diisopropyl fluorophosphate, have been found to have little clinical value. Recently two additional anticholinesterases have been subjected to clinical trial: Mestinon (pyridostigmine bromide) and Mysuran (Win 8077). Osserman (54) has reported that Mestinon is very effective in the relief of myasthenic symptoms. While its action during the day is only slightly longer than that of neostigmine, Mestinon appears to have a longer action during the night, frequently permitting the patient a full night of sleep. He has noted Mestinon to be definitely less toxic than neostigmine, and considers the drug more helpful in some patients than neostigmine. However, he considers that no drug or combination of drugs is effective when a patient is in a myasthenic crisis and resistant to neostigmine. Schwab (55) has reported the effectiveness of Mysuran (Win 8077) in the treatment of myasthenia, emphasizing that it is less likely to produce gastrointestinal symptoms than neostigmine. The duration of its action is about twice that of neostigmine and may last as long as six hours. Schwab does not recommend the parenteral use of this drug at present, and cautions with regard to the hazards of toxic reactions in view of the relatively longer duration of effect.

Despite the advances in the therapy of myasthenia gravis, the mortality rate remains high. Rowland *et al.* (56) have reviewed the course of 180 patients studied since 1930. The known mortality rate was at least 30 per cent. The average duration of symptoms among 39 fatal cases was 2.8 years. Thirteen patients died very suddenly and unexpectedly, suggesting the development of an acute myasthenic crisis. Sixteen patients were in a mechanical respirator at the time of death. Terminally, several patients showed little or no response to large amounts of neostigmine. The authors suggest that such patients may regain responsivity to the drug if there is a period of abstinence, while the patient is maintained in a mechanical respirator.

Respiratory infection frequently preceded the terminal crisis. Thymic tumor or hyperplasia was found in 15 of 26 autopsied cases. The occurrence of nodular myositis and evidence of myocarditis were also noted in a few cases. Complicating disorders included thyrotoxicosis and convulsive seizures in several patients. The authors emphasize several points in the management of such patients, including the hazards of barbiturates and other depressants in patients with ventilatory insufficiency, the recognition of premonitory symptoms of respiratory distress, the dangers of pulmonary infection, and the management of the myasthenic crisis.

The term "myasthenic crisis" is generally used to describe the rapid development of severe weakness of the muscles of respiration and deglutition, commonly requiring the use of the respirator. It is now recognized that at least two types of crises may occur: "true" myasthenic crisis due to insufficient medication or drug resistance, and "cholinergic" crisis, resulting from excessive medication (56a). Occasionally, crisis may be precipitated in patients with unsuspected myasthenia by the administration of curare-like substances for surgical and other purposes. Tether (57) has reviewed the management of myasthenic crisis and has emphasized the need for tracheotomy in patients with evidence of bronchial obstruction because of secretions associated with impaired coughing. With regard to differentiating between true myasthenic and cholinergic crisis, he recommends the following: if excessive secretions, miosis, or both, or relative bradycardia are present, 1.2 mg. atropine should be given intravenously. Atropine will relieve the muscarinic symptoms of overdosage with the cholinergic drugs but will not influence the weakness. If improvement does not result, 2 mg of edrophonium chloride (Tensilon) should be given intravenously and the needle left in place. If improvement occurs, the crisis is probably myasthenic, and a favorable response should follow increased dosages of neostigmine or other cholinergic drugs. However, the appearance of fasciculations would suggest that the crisis is cholinergic. If there is no effect within thirty seconds, another 0.8 cc. of Tensilon should be given. If no improvement, muscle fasciculations, or both follow, the weakness is probably due to cholinergic overdosage. It should be added that the Tensilon test has not been uniformly successful in differentiating one form of weakness from another (58). Rowland (58) has recently reviewed the problems of neostigmine-responsiveness in myasthenia gravis. Patients with a clinical syndrome identical to that described for myasthenia may never respond to neostigmine in diagnostic fashion.

The effect of thymectomy on the course of myasthenia gravis is not clearly established. Eaton & Claggett (59) have reviewed the Mayo Clinic experience and the English and American literature in this regard. They conclude that thymectomy has definitely beneficial effects in women under the age of fifty but that it is of no definite value in male patients. This is in essential agreement with the conclusions of Schwab *et al.* (60), although other reports are less enthusiastic with regard to the value of thymectomy. Eaton & Claggett (59) also observe that the removal of thymic tumors found

in association with myasthenia gravis in patients of either sex does not favorably influence the myasthenia. They do not recommend thymectomy in female patients if the disease has been present for ten or more years, particularly if it is stationary or improving. The evidence favoring a relationship between myasthenia and the thymus gland is derived from the high incidence of thymic tumor or "hypertrophy" in patients with this disease. However, the clinical data do not suggest that the thymus has a causal relationship to myasthenia. Eaton & Claggett (59) have proposed that there is a basic disturbance in endocrine metabolism which gives rise to both a defect in neuromuscular transmission and also to changes in the thymus gland. Final evaluation of thymic excision in the treatment of myasthenia will probably be difficult until the pathophysiology of the disorder is better understood.

The association of pregnancy with myasthenia gravis has been discussed by Osserman (61). He states that in 22 patients with myasthenia, having a total of 33 pregnancies, one third had a definite remission, one third had a definite relapse, and one third had no change in their myasthenic state. The pattern of the symptoms was usually established during the first trimester, and in all but two cases there was no significant change during the second and third trimester. Therapeutic abortion performed in six patients did not influence the severity of the symptoms. However, there was marked improvement in seven patients following spontaneous abortion. Labor and delivery were normal in these patients whenever adequate cholinergic medication was provided. Osserman also states that indications for cesarean section should be governed purely by obstetrical considerations. There were three cases in 16 live births in this series of transient neonatal myasthenia which disappeared within several weeks. These infants may require cholinergic medication during this period.

MUSCULAR DYSTROPHY

Research in muscular dystrophy, although thus far unrewarding in terms of therapy, has been in large part directed towards the metabolic defects associated with the disease. There are four major biochemical disturbances in the muscle diseases which have been investigated: (*a*) creatine metabolism, (*b*) electrolyte metabolism, (*c*) pentosuria, (*d*) serum aldolase and other enzymes concerned with glycogen metabolism.

The large volume of clinical data with regard to the creatinuria associated with the dystrophies has been recently summarized by Milhorat (62) and will not be covered by this review. The studies of Benedict *et al.* (63) have revealed that the urinary creatine commonly associated with muscular dystrophy does not originate in muscle but represents creatine newly synthesized in the liver which has been denied access to muscle. These data were obtained by measuring and comparing the concentration of N^{15} in urinary creatine and creatinine in two patients fed N^{15} labelled glycine while on a creatine-free diet. Initially far higher concentration of the

isotope was found in creatine than in creatinine, and the urinary excretion of N^{15} creatine was more rapid than that of N^{15} creatinine, indicating that creatine is excreted because it is not utilized by dystrophic muscle.

Shy and co-workers (64, 65) have studied electrolyte metabolism in the residual muscle of patients with muscular dystrophy. They have demonstrated an increase in the sodium content and a decrease in the potassium content of biopsy samples of dystrophic muscle tissue. These changes were correlated with a decrease in residual fiber water. Methods for the measurement of the exchange of potassium in the whole human body and in muscle were established using K^{42} as a tracer. A decrease in the turnover of potassium in the whole body was demonstrated, but the potassium exchange in dystrophic muscle was within the same range as normal muscle. These workers have concluded that the dystrophic patient has a lower rate of potassium turnover because of reduced total body potassium content and not because the turnover in the dystrophic muscles is altered. Thus they consider the low potassium concentration of dystrophic muscle as a consequence of the disease rather than as an etiological factor.

Blahd *et al.* (66) have also studied electrolyte metabolism in patients with muscular dystrophy and myotonia dystrophica. Using tracer techniques they have measured the "exchangeable" sodium and potassium of the body. Their data revealed no abnormalities of sodium exchange but a significant reduction in potassium exchange. Abnormally low values of potassium exchange were also noted in three healthy male siblings of patients with muscular dystrophy. There was a good correlation between exchangeable potassium, creatinine excretion, and physical disability in most patients with muscular dystrophy, but the correlation was poor in patients with myotonic dystrophy.

Several years ago, Minot *et al.* (67) reported the occurrence of a pentose in the urine of patients with muscular dystrophy. This pentose was identified as a ribose and was not noted in association with other neuromuscular diseases. However, a test for ribosuria was reported to be of no value in the diagnosis of muscular dystrophy by Walton & Latner (68) who reported 89 cases of which only 12 patients had ribosuria. Drew & Selving (69) also noted pentosuria in dystrophic patients as well as in patients with other neurological diseases, and were cautious in attributing any specificity to this finding. Ronzoni *et al.* (70) found no free ribose in paper chromatograms of urine from 20 dystrophic and 20 control patients, but observed ribose in most specimens after hydrolysis, presumably representing nucleotide bound ribose. However, these results have been criticized on the basis of their technical methods of analysis (71). Tower *et al.* (71) have studied quantitatively the urinary excretion of free pentose (aldopentoses) in patients with muscular dystrophy and other myopathies, and have further identified the various carbohydrates using two-dimensional paper chromatography. The 24 hr. excretion of free pentoses of patients with myopathies was about twice that of the control group. In the myopathic group ribose predominated, but in the control groups arabinose was the predominant urinary pentose. No cor-

relation could be established between these findings and the clinical status of the patients (based upon duration of disease, rate of progression, degree of muscle involvement, histopathology, and electromyography). However, the amount of pentose excreted did correlate with the "functional residual muscle mass" as estimated by radioactive potassium exchange. The authors suggest that the urinary excretion of pentoses (chiefly ribose), increases as the functional residual muscle mass is reduced in the progression of the various myopathies studied.

The occurrence of increased concentrations of glycogenolytic enzymes in the serum of patients with muscular dystrophy has been reported by Schapira *et al.* (72). They noted an increase in serum aldolase in 71 of 76 patients. An increase was also noted in acute poliomyelitis and in myotonia atrophica but no changes were noted in other neuromuscular diseases. Hyperaldosemia has also been noted in patients with cancer, leukemia, gout, and obstructive jaundice. The serum phosphohexoisomerase level was also noted to be increased in dystrophic patients but less constantly and to a lesser degree than the aldolase. In addition, a reduction in aldolase, phosphorylase "a" and "b", phosphoglucomutase, and overall glycogenolysis was noted in muscle tissue from dystrophic patients. No relationship was found between the plasma levels of aldolase and the degree of muscle involvement or duration of the disease.

A hereditary primary myopathy in mice has been reported (73). Histopathologically the myopathy is similar to human muscular dystrophy. The occurrence of an experimental animal with a genetically determined myopathy similar to that in the human should provide a very valuable research tool in studying the nature of the myopathies.

PARKINSONISM

Several new drugs have been reported to be useful in the management of Parkinsonism. These include cycrimine (Pagitane) (74), ethopropazine hydrochloride (Parsidol) (75), procyclidine hydrochloride (Kemadrin) (76), and benztropine (Cogentin) (77). The effectiveness of these agents does not appear to differ greatly from other preparations in common usage. The administration of chlorpromazine and reserpine in high dosage has been reported to induce a syndrome very similar to that of Parkinsonism, which disappears when the drugs are withdrawn (78). This finding warrants caution in the administration of the drug to patients with this disease.

A wide variety of surgical procedures has been used for many years in an attempt to inhibit the abnormal movements and changes in muscle tone characteristic of diseases of the basal ganglia. The results obtained following surgery were disappointing and the operations did not gain wide acceptance. Improvement, when noted, was generally related to injury to the corticospinal system which substituted a hemiplegia or hemiparesis for the more disabling extrapyramidal symptoms. Frequently, with the disappearance of the hemiparesis the former symptoms would return, and progression of the disease would continue (79).

Recent techniques have attempted to destroy portions of the basal ganglia, particularly the globus pallidus and its outflow in an effort to inhibit the extrapyramidal symptoms.

Fénelon (80) has reported on the coagulation of the ansa lenticularis in 60 patients with Parkinsonism followed postoperatively for six months to four years. He describes favorable results in 70 per cent.

Narabayashi, Okuma & Shikiba (81) have injected the globus pallidus with procaine in oil and wax in 26 patients with Parkinsonism. They report improvement in tremor and rigidity in all cases, but the tremor tended to return to its former level in several weeks. One operative death and several cases of postoperative hemiplegia were described.

Guiot & Brion (82) have destroyed the pallidum in 81 patients using various techniques. In their more recent group of 40 patients, they report a favorable result in 60 per cent. Complications included confusional states and aphasia.

Cooper (83) has reported that occlusion of the anterior choroidal artery resulted in marked improvement of tremor and rigidity in 30 of 50 patients. The operative mortality was 10 per cent and 3 patients developed hemiplegia. More recently he has attempted to destroy the globus pallidus directly by the injection of alcohol (chemopallidectomy). In 1956 (84) he summarized his results in 50 patients. The operation was beneficial in 65 per cent of cases. There were two deaths, one postoperative hemiplegia and one case with ataxia and oculomotor nerve palsy.

MISCELLANEOUS DISORDERS

Behçet's Syndrome

Behçet's syndrome is characterized by relapsing iritis, often with hypopyon, and recurrent attacks of oral and genital ulceration. Pallis & Fudge (85) have reviewed the neurological involvement associated with this unusual syndrome. There have been four deaths in the 13 cases reported with involvement of the nervous system. Neurological complications generally occur between the second and fifth year of the disease and usually conform to one of the following patterns: (*a*) A brain stem syndrome, which may be episodic or irregularly progressive, resulting in fatal bulbar paralysis; (*b*) A meningomyelitic syndrome characterized by recurrent attacks of paraplegia or quadraplegia associated with fever, headache, meningeal signs and marked polymorphonuclear pleocytosis in the spinal fluid. Transient or terminal brain stem symptoms may also be noted; (*c*) An organic confusional syndrome, which may be transient or progressive to a severe dementia associated with convulsions. Review of the pathological findings does not support the hypothesis that Behçet's syndrome is due to a vascular disorder associated with multiple thromboses, nor is there evidence of an "allergic encephalomyelitis." The authors suggest that a virus infection, occasionally neurotropic in nature, is the cause of the illness. The presence of an abnormal increase in plasma fibrinogen was also noted.

Collagen Diseases

Glaser (86) has reviewed the neurological manifestations of the collagen diseases, including systemic lupus erythematosus, scleroderma, periarteritis and dermatomyositis. The neuropathological findings in these diseases are usually secondary to characteristic proliferative and degenerative changes in the connective tissue of small blood vessels of the central nervous system and the peripheral nerves. The vascular changes, although variable in detail in these diseases, are associated with disseminated ischemic and hemorrhagic lesions in the nervous system. In dermatomyositis and polymyositis there is direct involvement of muscle tissue. The distribution of the lesions in the collagen diseases is variable. In systemic lupus erythematosus there are disseminated focal lesions in the cerebral cortex, particularly in the perisulcal regions of the grey matter, which probably accounts for the high incidence of convulsive seizures in this disorder. Involvement of peripheral nerve is rather uncommon in systemic lupus. In contrast, the vascular lesions of periarteritis frequently involve the peripheral nerves, causing single or multiple peripheral nerve palsies. In periarteritis, the vessels of the cerebrum are also commonly involved resulting in focal neurological deficits. Rarely, periarteritis may be associated with interstitial keratitis, deafness and vestibular symptoms (Cogan's syndrome). In dermatomyositis, the lesion involves the skin and muscle primarily, and generally spares the central nervous system. In scleroderma, the involvement is mainly of the peripheral vascular system, with possible sympathetic involvement as basis for the Raynaud's phenomenon. It is of importance to note that in some patients there may be generalized involvement which makes clinical and pathological differentiation very difficult.

The concept of polymyositis has been broadened recently. It is characterized by symmetrical weakness of the muscles, particularly those of the shoulder and pelvic girdles without evidence of any other systemic disease. The symptoms and signs may closely resemble those of the adult forms of muscular dystrophy. Diagnosis may be established by muscle biopsy and the presence of electromyographic evidence of muscle degeneration. Polymyositis may also occur in association with the skin lesions of dermatomyositis and scleroderma, and with rheumatoid arthritis.

Glaser (86) points out that the natural course of collagen diseases may be extremely variable. Spontaneous remissions or exacerbations, often of long duration, may make evaluation of therapy difficult. Cortisone and corticotropin have been widely used in the management of these disorders. While improvement has been noted, these agents are suppressive in nature and not curative.

Polyneuritis

Although many specific etiologic factors have been associated with various clinical forms of polyneuritis, the etiology of acute idiopathic infectious polyneuritis (Guillain-Barré Syndrome) has been a mystery. Recent

experimental evidence of Waksman & Adams (87) has given support to the supposition that this clinical entity may have an "allergic" or immunologic basis. Following the injection of rabbits with a mixture of rabbit spinal cord, killed tubercle bacilli and mineral oil, they observed the development of multiple areas of myelin degeneration and inflammation throughout the central nervous system, nerve roots, spinal ganglia, and peripheral nerves. This entity has been referred to as experimental allergic encephalomyelitis. When rabbit sciatic nerve is used as the antigen in rabbits, lesions occur only in roots, ganglia, and peripheral nerves. There are no lesions in the central nervous system, nor in the meninges. This disease picture in rabbits has been termed experimental allergic neuritis. Sciatic nerve of other mammals produces the same disease in rabbits as does rabbit nerve, and the antigenicity of nerve is not destroyed by autoclaving. The animals develop a picture suggestive of a flaccid quadriplegia. The spinal fluid of these animals has a high protein content but the cell count is usually normal. These findings are reminiscent of the albumino-cytologic dissociation of the Guillain-Barré Syndrome. The pathological findings in the animals resemble the changes seen in fatal cases of infectious polyneuritis. The mechanisms whereby hypersensitivity to an antigen composed of myelin can induce such changes have not been determined. The relationship of this experimental syndrome to the clinical entity infectious polyneruitis is uncertain.

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PSYCHIATRY[1]

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It is evident that research in psychiatry is coming of age. Adequate investigative methods are gradually evolving, and progress in psychiatry is slowly being related to the growing understanding in the whole field of human biology. The descriptive and the doctrinaire in psychiatric research are happily giving way to a more detached attitude of inquiry. Since progress in the whole field during the past year cannot be encompassed within this short review, it will deal mainly with the most rapidly advancing frontiers and with certain important developments which bear fairly directly on the field of internal medicine.

Bodily Symptoms and Disease

In the past and up to midcentury, sufficient experimental evidence had accumulated to establish that a wide variety of bodily organs and organ systems are capable of reacting to symbolic stimuli with the manifestations of disease. A list of bodily structures capable of such reaction takes in virtually all of the organic equipment of man (44). The inference is that man's organs are connected in some way to the interpretive areas of the brain and are thereby capable of reacting to impulses which emanate from these highest integrative neural centers. It has been pointed out that the brain is

> capable of enhancing, altering, diminishing, or even suspending the functions of organs or cellular systems which might otherwise proceed automatically. The extent to which it is capable of influencing the entire internal economy is not generally appreciated and it is probably for this reason more than any other that the effect of adaptive reactions upon human health is often underestimated (44).

Correlations of visceral and other organic behavior with life experience and emotional responses have continued to appear in the literature. Female infertility has been related to failure of the anterior pituitary to release luteinizing hormone under circumstances of chronic psychological maladjustment (34). Similarly the occurrence of habitual abortion in women has been related to situationally determined disturbances in uterine motility manifested particularly by premature dilatation of the cervix (66). Correlations have also been reported with the urinary excretion of formaldehydogenic steroids and creatinine (90), in finger blood flow (10), capillary pressure (58), circulating eosinophils (41), and in the regulation of water and electrolyte metabolism (89). Confirmatory data have been derived from animal experimentation. In female dogs stimuli which appeared to be emotionally disturbing induced increased uterine contraction associated with inhibition of water diuresis (1).

[1] The survey of literature pertaining to this review was completed in August, 1956.

In measurements of hemodynamics in humans, Funkenstein observed the secretion of epinephrine-like and norepinephrine-like substances under different circumstances of stress (31). King & Henry (48) related these changes to the subjects' relationships with their fathers. Strict and dominant fathers correlated with norepinephrine-like reactions, while the children of mild fathers more often displayed epinephrine-like responses. Sulkowitch further found evidence that the output of the urinary epinephrines in anxiety may equal or exceed the quantities excreted in patients with pheochromocytoma (96). In a monograph on essential hypertension and other circulatory adaptations, Wolf and associates reported experimental documentation of a variety of hemodynamic effects (in addition to the epinephrine-like and norepinephrine-like responses) as part of man's adjustment to people and events of significance in his daily life (105). Fowler & Zeckel observed a hydrops of the endolymphatic structures in the inner ear under circumstances of repressed, aggressive feelings (28) and Bilisoly and associates actually induced tissue damage secondary to vascular changes occurring in response to symbolic threats (11). These authors confirmed and extended the work of West who, using hypnotic suggestion, was able to either mitigate or aggravate both the subjective reaction and the actual tissue damage to noxious and non-noxious stimuli (99, 100). In this connection the case described by Harris is of special interest (46). An army officer during abreaction under psychotherapy suddenly developed on his wrists the marks of ropes with which he had been tied during captivity ten years before. This observation establishes vividly the relation between perception and reaction and illustrates that in the case of "deeply grooved" patterns the effector mechanisms remain responsive to perceptual stimuli even when they arrive only from recollection. These and other similar studies serve to strengthen the already widely held proposition that bodily adjustments, including disease processes, may be set in motion by events or circumstances which owe their force to their particular meaning to the individual.

Psychodynamics

Although many physiologic and physiopathologic changes occurring in response to meaningful life situations have been identified, and some of the mechanisms tentatively spotted, the elucidation of the psychological determinants of the bodily changes is still bogged down in controversy and uncritical assumptions.

Some have felt that the pattern of bodily response is largely an expression of the individual's aims and goals and hence is the result of an acquired psychobiological need. Others, more concerned with innate needs and drives, have related the nature of the bodily response to the arrest of emotional development at various levels. Still others have not recognized any specific psychological relationships and have thought of the nature of the bodily pattern as more or less accidental, perhaps related to conditioning and perhaps involving built-in constitutional proclivities or vulnerabilities. Whether related to inborn characteristics, personality development in in-

fancy and childhood, or whether shaped by social adaptations over the years, there is a strong body of opinion which holds that the behavior and emotional aspects of personality correlate with biochemical and physiological functions (103). Although the general failure to establish personality correlates for the various types of disturbances has been interpreted as evidence for lack of specificity, it is equally plausible that the presently available testing procedures are not sufficiently sharp to make the required distinctions.

Ring attempted to test the hypothesis that recognizable individual personality characteristics correlated with various disease patterns (86). He accordingly interviewed a series of 200 patients without knowing the diagnosis and without discussing symptomatology. He found that he could identify with a significantly high correlation those with coronary heart disease, peptic ulcer, essential hypertension, rheumatoid arthritis and ulcerative colitis. Grinker & Robbins described certain common denominators among individuals with multiple sclerosis (35), and Knapp and his associates found characteristic personality features among those with bronchial asthma (49). Correlates, although uncontrolled, have even been identified in patients with cancer (55), and those interested in the pathogenesis of infectious diseases are turning their attention towards the characteristics of the host which make infection likely or unlikely (63). So far, however, there is only fragmentary evidence of the relevance of personality adjustments to susceptibility to infections.

Social Pressures

Dubos, after an exhaustive study of possible correlates with outbreaks of tuberculosis in various parts of the world over several centuries, concluded that the closest correlation was with what he referred to as social upheaval. This correlation was closer than that individually for famine or war or crowded conditions of living (21). Hollingshead & Redlich noted an increase in neurotic and schizophrenic illness in association with the socially upward mobile segment of the population (47). Stewart, Webb & Hewitt made a study of the presence of illness among various social classes (93, 94, 95). Rennie & Srole also correlated incidence of illness with social class (83). So also did Quinn (82), Buell (16), and Lemkau (54). Leighton (53) studied circumscribed communities and Fish (25) reported increased incidence of minor maladies among school children with impaired intelligence. Basowitz & Grinker and associates pointed up the potential pathogenic significance of present day social pressures when they found greater disturbances among paratroopers in training when they feared the low regard of their associates than when they were afraid of bodily injury from jumping (7).

The enormous importance of nourishing social experiences to the adequate adjustment of man to his environment has been vividly pointed out by a study of the interrogation methods used by the Russian and Chinese communist police states (43). It was observed that the need of human beings

for approval and for the opportunity to relate in some way to others and their sensitivity to rejection was sufficient to elicit false confessions after prisoners had been confined under hopeless circumstances and isolated from all except their interrogator. Man is a social animal whose welfare appears to depend upon the adequacy of his social climate as well as upon the other variable aspects of his environment.

In general, in the social studies physiological adjustments seem to correlate better with morale and the adequacy of social adjustment than they do with any particular social pattern or constellation. In this connection, it is interesting that those spending part of their lives on the polar wastes of Antarctica report a virtual freedom from disease (70).

Currently the most widely held point of view is that the biological response to a situation depends not only on individual adaptive capacities but also on the way the individual perceives the circumstances and how he sees himself in relation to them. This interpretive function may, of course, be unconscious or a subject may be dimly or partly aware of his complex attitudes toward a given situation. The situation appears to be stressful, however, according to the degree to which it threatens him or taxes his adaptive capacity.

It should be noted, of course, that stressful circumstances do not necessarily provoke destructive adjustments or disease. Important discoveries, works of art and advances in thought have also been made in reaction to stressful circumstances (104). Reaction to stress may thus be measured in terms of achievement and the development of new potentials, in terms of the maintenance of equilibrium, or in terms of the failure of adaptation, behavior disturbances and disease.

It would appear that certain situations evoke a sufficiently uniform type of response among persons in our cultural pattern that some degree of correlation may be made between situation and type of response. Conversely it has been possible to observe contrasting effects in situations whose stressful significance to those in our culture is grossly different. Striking along this line are the studies of Groen who observed that his patients with active peptic ulcer prior to the German occupation of Holland lost their symptoms in the dismal and depressing situation of the concentration camps but regained them after the Allied victory when they were returned to their former places in their communities (36). These findings led Whitehorn to suggest that the goal of therapy should not be the avoidance of stress but rather the organization of life toward energetic and rewarding effort in stressful situations (101). He pointed out that keeping healthy implies a successful adaptation to challenging and adverse circumstances of all types rather than avoiding them by achieving a literally and figuratively aseptic environment. A generally unstable atmosphere, however, appears to impair adaptive capacities toward specific events. Thus Schottstaedt and his associates, studying metabolic adjustments in patients on a metabolic ward, found that events considered to be stressful were associated with significant deviations in excretion of nitrogen, water, and electrolytes twice as frequently when

they occurred on days when the ward was upset than at times when the general atmosphere of the ward was stable and reassuring (88). The importance of the stability of "home base" to the adaptive capacity of the individual in intellectual as well as visceral functioning was shown by the studies of Chapman & Wolff who tested intellectual adaptations in individuals with and without brain injury (17). Performance on problems involving learning was notably poorer when the circumstances of the subject's life were somewhat unstable at the time of testing. An individual's ability to function effectively is deeply affected by what the situation offers or demands of him. The importance of individual social values and attitudes in adjusting to handicaps has been sharply pointed up by the work of Dyk & Sutherland who found among their patients with colostomy a wide range in the degree of incapacity conferred by the operation depending upon the earlier attitudes and adjustment patterns of the patient (22).

Social pressures together with personality attributes and situations appear capable of affecting an individual's health depending how he consciously or unconsciously perceives and evaluates a given situation in the social setting in which he finds himself and in view of his unique experience and personality characteristics. It is to be expected that his reaction pattern would correlate in only a limited way with any one of these factors.

Lessened preoccupation with a unitarian concept of cause has allowed for greater understanding of the ecological concept of disease as a maladaptation of the individual to his environment. Hinkle and associates in a study of three distinct but homogeneous groups found that the majority of diseases of all sorts occurred in a minority of individuals, namely that segment which was maladapted with respect to situational satisfactions and the realizations of goals (45).

Genetics

Individual susceptibility to bodily disturbance and disease has also drawn considerable interest from the field of genetics. Aird (3), Koster (51), and most recently Buckwalter and associates (15) have confirmed the early findings of Buchanan & Higley (14), that susceptibility to duodenal ulcer is linked with blood type. Mirsky found evidence of an inborn excessive gastric activity in those who develop peptic ulcer (68), and Richmond & Lustman observed a broad difference in a variety of autonomic functions in recently born infants (84). Even Franz Alexander, who had been one of those most prominently interested in the relation of specific conflicts to specific disease patterns, found evidence of a strong contributory genetic proclivity (4). The relevance of genetic factors to the pathogenesis of essential hypertension has recently been reviewed by Pickering (76) and to schizophrenia and various neuroses by Gerard (33).

Neurochemistry

Perhaps the largest number of publications relating to progress in psychiatry has concerned chemical, endocrine, and pharmacologic studies.

Definitive information on neurochemistry and neuropharmacology is

fragmentary but research is so active on half a dozen fronts that it is almost impossible for one person to follow and integrate the process. Several monographs have appeared during the past year on this general subject (2, 6, 18 24, 27, 30, 50,). The developments generally confirm earlier notions that locally elaborated chemicals are important to the mediation of neural impulses.

Great impetus for progress in the field derived from the discovery by Hild & Zetlar that the human brain is actually capable of elaborating internal secretions which may influence other structures via the circulation of the blood (40). The complexity of the interrelationships is suggested by the work of Brull & Louis-Bar, who found evidence that the hypophysis secretes a substance which enables the vasculature of the kidney to adapt to variations of intravascular pressure (13). Olivecrona found that the paraventricular nuclei in the hypothalamus played a part in regulating the production of oxytocin by the posterior lobe of the pituitary (74).

Friedgood (30) and Cleghorn (19) have emphasized the interrelationship between neural hypothalamic connections and endocrine activity, particularly of the pituitary. There is mounting evidence, however, that the pituitary-adrenal axis, important though it may be in mediating bodily responses to meaningful life situations, is only one of several possible operating mechanisms. With respect to the lack of adrenal participation in all of the stress mechanisms, the findings of Larsen & Lassen are relevant (52); they concluded that the hypoferremia of stress is independent of the function of the adrenal cortex. At the present time there are several hormonal substances believed to be secreted in this fashion, including epinephrine which appears to be locally elaborated and utilized as part of an enzyme mechanism within the cerebral tissue (30). In any case other enzyme systems, including acetylcholine and cholinesterase are enormously important to cerebral metabolism (42).

Nurnberger & Gordon studied changes in the "labile N_2 pool" in the brain and liver of rats (71). They concluded that adrenocortical activity is responsible for the ready availability of N_2 during stress and therefore mental functioning. Serotonin is apparently another important chemical mediator in the higher centers of the brain which affects O_2 consumption (20) and the electrical activity of various parts of the brain as well as behavior in animals and humans (32, 69). Amin and associates (5), and Paasonen & Vogt (75) studied the concentration and distribution of normally occurring serotonin (5-hydroxytryptamine) in various areas of the central nervous system. High concentrations occur in brain areas including those intimately related to both autonomic and the reticular activating system, the same general areas where high concentrations of epinephrine and norepinephrine are found (98).

Further importance of serotonin derives from the finding that it antagonizes the hallucinogenic agent lysergic acid diethylamide (LSD) in animal and human studies (67, 69, 92). Vogt and associates (97) found that the antagonism of these drugs was most marked in the basal ganglia and in

projections of the limbic system. Both compounds caused additive depression of midline brain stem areas. Associated fluctuations in blood pressure were seen with both compounds. The work of Pletcher, Shore & Brodie indicates that reserpine acts by liberating serotonin from the brain (77). The implication is that serotonin itself is an important agent in neural functioning. The evidence of Wikler, however, indicates rather that the central action of serotonin may be attributable to its effects on vascular structures (102). Shaw & Wooley have also called attention to certain similarities in the effects of the agents (91).

The studies of Purpura (79, 80, 81) focus on the cellular and synaptic level of electrophysiological facilitatory and depressing changes induced by LSD and reversed by reserpine. His work and that of others on the various levels of change in the central nervous system neural patterning underlying drug-induced perceptual alterations may clarify some of the basic mechanisms in mental disorders. Most investigators have been led to conclude that whatever disrupting effects occur from serotonin or the tranquilizing agents on cerebral function occur on the afferent side involving fibers from the hypothalamus to the cortex and only partially the reticular projection system of Magoun. The work of MacLean suggests that reserpine activates subcortical areas of the rhinencephalon which may in turn be responsible for inhibiting the transmission of impulses to and from the integrating symbolizing neocortex (62a). Similar evidence exists for chlorpromazine which was found to stimulate the amygdaloid area of the rhinencephalon (78).

Unfortunately the promising fruits of chemical research have given rise to specious argumentation concerning the etiology of mental illness. By confusing cause with mechanism, many workers have fallen into the trap of predicting that the life experience and emotional life of the individual will be found to have no bearing on such disorders as schizophrenia because they appear to be chemically mediated. This is an extraordinary inconsistency of thought in the face of the familiar data on such disorders as peptic ulcer which are also chemically mediated but whose chemical disturbances appear to be set in motion as part of the individual's pattern of dealing with troublesome people and events in his day-to-day life.

The largest number of psychiatric papers published during the past year has dealt with the new tranquilizing drugs. Unfortunately, however, there is no clinical evidence of the first order to indicate just what these agents do. Almost anything that is undertaken enthusiastically as medical therapy appears to be enormously effective for a time, occasionally for a very long time. Thus bleeding appeared to have value in the treatment of pneumonia, gastroenterostomy in the treatment of peptic ulcer, and so forth. These intrinsically inert therapies have been endowed through the faith of physicians with powerful and often misleading placebo effects. As Louis Linn stated in his "Handbook of Hospital Psychiatry" published during the past year, "It has been observed frequently that new therapies destined to be discarded as ineffective seem to produce a favorable response in patients when first tried. It is likely that the therapeutic efficacy stems more from the con-

cern and interest of the physician than from the ingredients of the agent used" (57). Currently the value of adrenocorticotrophin and cortisone in arthritis therapy is being soberly reviewed. It is likely that the spectacular popularity of the tranquilizing or ataraxic agents will require similar critical study. Since so many questions remain unanswered, it is fortunate that the Veterans Administration is taking the lead and planning a cooperative study of the values and potentials of these agents in psychiatric patients.

Not only do pharmacodynamic therapies require detachment and careful control in their evaluation but so also do the various psychotherapies. Rosenthal & Frank pointed out that the only adequate control for psychotherapy is another form of therapy in which the patient has equal faith so that the placebo effect will operate equally in both (87).

There is a real danger if the use of tranquilizing agents becomes so widespread and promiscuous that the physician feels that a written prescription can allow him to side-step his responsibility of getting to know his troubled patients and understanding them.

The introduction of the new tranquilizing drugs has provided an opportunity to study the effects of these agents on other chemical mediators and to observe their distribution in brain tissue as well as their effects on psychological functioning and general behavior. Available methods of study are so gross at the present time, however, that there are naturally many conflicting interpretations of findings and, as is usual in an active area of research, speculation has far outrun the data.

Neural Organization

The ultimate key, of course, involves fathoming the secrets of central nervous organization. If adaptive processes all over the body involve integration by the highest neural centers, failure in adaptation, or disease, would appear to imply a disturbance in the organization and integration of sensory, motor, autonomic and cognitive functions in the brain. It is known that these processes may be impaired by reduced oxygen concentration secondary to a variety of causes including high altitudes, vascular deficiency and so forth. They can also be disturbed by chemicals which presumably interfere with normal enzymatic and other metabolic processes. Trauma and perhaps electrical currents are similarly capable of altering the organizational setup. The way in which the disturbing effects of frustrating and anxiety-producing situations are mediated in the nervous system is not known, but it is clear enough that disturbances occur in cortical, subcortical, and brain stem connections which presumably modify responses to afferent stimuli. It has been shown that when one sensory modality is dominant, impulses from another sensory area may be inhibited via the mechanisms in the reticular formation. For example in the cat the smelling or sighting of a rat inhibits the cochlear nucleus potential following a stimulation by sound (39). In humans the perception of a second sensory stimulus is blocked to the greatest extent in those who have sustained cortical damage (9). Changes in electroencephalographic patterns from cortical and subcortical areas have

been reported in response to epinephrine infusion, splanchnic stimulation, or carotid sinus stimulation in animals (12). Such alterations in electroencephalographic pattern have been further correlated with "spontaneous" and stress-induced fluctuations in blood pressure. Other cardiovascular disturbances including arrhythmias have been produced by hypothalamic and brain stem stimulation, and the effects have been blocked by reserpine and chlorpromazine (37).

The refinement of stereotaxic technics so that small areas of brain can be stimulated or recorded from has greatly accelerated progress. It has even become possible to undertake chronic cortical stimulation in animals which can be kept alive and studied almost indefinitely. French and his associates were able to produce gastrointestinal lesions, including ulcers, in monkeys subjected to chronic stimulation in the neighborhood of the hypothalamus (29) and the work of Maire & Patton implicates the preoptic nuclei in the mechanisms of gastric erosions, pulmonary edema, and certain behavior changes in animals (65). Fisher induced maternal and sexual behavior in animals by intracranial stimulation by chemical means (26).

It would appear that activity in these areas modulates or modifies the way in which reactions to afferent stimuli are formulated in the highest integrative levels of the nervous system. The capacity to react to any type of environmental stimulus seems to require the presence of some sort of afferent or sensory equipment. Friedgood has called attention to the studies of several workers who found striking and widespread bodily changes in animals and man which follow a variety of sensory stimuli and which constitute a part of the organism's interaction with the environment (30).

1) Exposure to an uninterrupted source of bright, artificial illumination, which does away with the hours of darkness, activates the ovaries and brings about estrus in the non-estrus cat, hen and ferret by virtue of its effect upon the diencephalo-adenohyophysial system which elaborates the necessary gonadotrophic hormones. 2) Specific changes in the chemical composition of pond water precipitates spawning in the common frog, presumably in response to their effect (initially) upon cutaneous chemoreceptors. 3) Ovulation occurs after mating in the cat, rabbit and ferret as the immediate result of the animal's sensory and emotional experiences during the course of coitus. These psychosensory experiences activate the gonadotrophic component of the diencephalo-adenohypophysial complex, as a consequence of which the ovarian follicles mature. Ovulation does not ordinarily occur in these species other than after coitus. 4) Touching the cervix uteri of the cat, rabbit or rat with a glass rod activates the neuro-endocrine gonadotrophic mechanisms of the adenohypophysis as a result of which ovarian follicular luteinization and pseudopregnancy occur. 5) Physiologically tolerable extremes of temperature produce hyperactivity of the avian and mammalian thyroid gland in a cold environment and hypoactivity under torrid climatic conditions, both of which are mediated by the neuroendocrine system. 6) Startling or frightening auditory, visual and social experiences, or somatic pain, stimulate the adrenal medulla to secrete epinephrine.

Lovett Doust & Schneider showed that peripheral capillary oxygen saturation could be raised or lowered at will by altering the frequency of the

flickering light. This very predictable reaction they called the photic flicker profile (60).

Not only do automatic and altogether predictable responses occur, presumably mediated through a relatively low integrative level but so also do responses which require interpretation of the afferent stimulus or experience. It may be that ordinary day-to-day adjustments of the human organism depend upon a more or less constant barrage of afferent impulses of various types.

Lilly immersed himself in darkness in warm water in order to reduce sensory input and experienced marked mental aberrations (56). In the studies of Olds and associates (72, 73) apparently "pleasurable" or "reward" stimuli were self-introduced by the animals through electrodes implanted into the septum and neighboring areas of the brain. They observed that the drive to pleasure apparently took precedence over that toward alimentation and survival. Heath from studying animals and humans with chronic implants has evolved an hypothesis of dual circuit control of thought level, one pathway facilitating and the other inhibiting (38). MacLean has studied the relevance of connections in the rhinencephalon to the organization of emotional, autonomic and behavioral patterns in animals (61, 62b). He found evidences of connections between this "limbic" system and the reticular formation. Magoun had shown earlier that stimulation of the reticular system activates the cerebral cortex increasing the general level of awareness (64). Awareness has been linked to oxygen saturation in peripheral tissues by Lovett Doust & Schneider (59). They showed that a variety of auditory and visual stimuli were capable of affecting this level of awareness.

The importance of neural responses to meaningful events is emphasized by the work of Richter (85) and Bauer (8) who found evidence of sudden death in humans and animals brought about by excessive vagal activity and consequent disturbance in conduction in the heart with cardiac arrest. The multiplicity of areas in the brain capable of initiating or transmitting impulses which affect visceral behavior was pointed out by the work of Eliasson, who was able to identify as many as 15 different areas which when stimulated increased gastric motility and 8 areas stimulation of which caused inhibition (23). He found efferent pathways in both the splanchnic and vagus nerves and found that the excitory effects could be abolished by atropine.

The gathering evidence of complexity of organization in the brain of activity in one area inhibiting transmission in another, of the extent of transaction at various levels before a response is set in motion has all but done away with older concepts of cerebral localization as related to either visceral or general behavior. Indeed the nature and degree of the loss of intellectual assets after lobotomy seems to be more clearly related to the quantity of tissue destroyed than to the localization of the lesion (17).

The ultimate implications of all these studies to the general field of medicine are several, having to do with disposing of straw men and beginning the elimination of needless semantic barriers. The linking of enzyme systems

and electrical activity of the brain with feelings and behavior begins to eliminate the artificial distinction between psychological and physiological. It has also reminded us that all of man has structure and all structures have functions, hence dispensing with another old chestnut that has caused endless confusion. Simply stated we now have good evidence that, within the proclivities of his native endowment and in the framework of his past experience man's motivations, goals, attitudes, and conflicts are capable of modifying receptor activity in the highest integrative centers of the brain. The modifications may occur in such a way that responses are formulated which can involve almost any organ of the body thus producing symptomatic disturbances by themselves or altering the body's ability to adapt to other noxious forces. It should be no surprise to learn that these modifying or integrative processes at the highest neural levels should be mediated through chemical transformations and electrical activity. It should be equally predictable that the processes are capable of modification by pharmacodynamic agents. Disease thus becomes a way of life, as physical as man himself, as structural as his parts and as functional as the process of living.

A major question for the future is: how much do all disease processes require integration at a neural level, hypothalamic or higher? In pneumonia, for example, we recognize the disease as an interaction between a unicellular plant and a multicellular mammal. Most of what we see of pneumonia is in the alveolar air spaces. The alveolar walls themselves contain dilated capillaries, but we recognize pneumonia under the microscope by dense collections of white blood cells, blood serum and a few red cells in the alveoli. Surely this must reflect a disturbance in the relatively distant bone marrow in view of the greatly increased number of white blood cells in the circulating blood. The lymphoid tissue throughout the body, which appears to synthesize immune globulins, is also implicated. Pneumonia is characterized by fever, which if the process is undisturbed by antibiotics, continues for a certain number of days and then drops suddenly, thus implying involvement of the brain stem temperature regulators in the overall integrative process of the disease. Pneumonia could as readily be considered a vascular disease as a pulmonary one, for in the lungs the lesion is the result of vasodilatation with changes in capillary permeability and seepage of blood elements into the air sacs. In reality, pneumonia is a whole body response. It is not known whether or not the nervous system is responsible for integrating so beautifully this response.

The rapidly gathering data indicate that the human organism as a whole, with all its equipment is engaged in ever-changing reactions to contacts with the environment as mediated chiefly through afferent neural equipment. Thus the process of health or disease is a living continuum involving experience, interpretation and thought, as well as visceral and general behavior.

Research in psychiatry is now being done by anatomists, chemists, physiologists, pharmacologists, social scientists, and clinicians of all types. From this wholesome new atmosphere will come much favorable progress in the future.

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DISEASES OF THE RESPIRATORY SYSTEM[1]

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The purpose of this review is to draw attention to some of the important problems of current interest, particularly those which may be related to the inception and development of chronic disease. Since a full review is not possible in this chapter, a selection of references has been included to represent the trends of investigation and some of the prevailing views.

CHANGES IN STRUCTURE AND FUNCTION OF THE LUNG IN OLD AGE

A number of respiratory disorders occur with increasing frequency, severity and chronicity in the later years of life, some apparently related to anatomic changes inherent in or accompanying the process of aging. Richards (1), observing that the lungs of the aged are relatively small, flabby and light, notes a reduction of their elastic tissue components and of the lumens of small blood vessels. In the senile, nonobstructive type of emphysema respiratory function is fairly well maintained in spite of diminution of maximum breathing capacity and ventilation. Only during heavy exertion, demanding a large consumption of oxygen, does the septuagenarian fall far behind the younger person, and this deficiency is attributable chiefly to a progressive loss of cardiac and circulatory capacity. This type of emphysema, not explainable otherwise, may possibly be a result of some atrophic and degenerative process which is not necessarily a part of aging. The late E. M. Medlar (2), who palpated thousands of macroscopic sections of lungs, was convinced of differences of texture in specimens from different subjects, which perhaps suggests a genetic variation. Whether or not a very delicately constructed lung, young or old, may be more vulnerable to infections and other insults is questionable, e.g., the tendency of some persons to recurrent rupture of the pleura and pneumothorax has been so ascribed, but only by presumption.

ALVEOLAR CELLS OF THE LUNG, ALVEOLAR FLUID, BRONCHIAL MUCOSAL FUNCTION, AND SOME IMPLICATIONS

Employing electron microscopy and histochemical methods, Bertalanffy & Leblond (3) find support for the concept that the pulmonary "alveolar tissue is lined by epithelium composed of extremely attenuated squamous cells resting upon a basement membrane, and that the alveolar cells within

[1] The survey of the literature pertaining to this review was completed in August, 1956.

the walls are connective-tissue cells at various degrees of differentiation." Macklin (4, 5) believes that the alveoli are normally coated with a thin watery mucoid film (theoretically about 0.2 μ thick) and that it is formed from a hydrated secretion of the granular "pneumonocytes" which are assumed to be of endodermal origin; he also believes that an excess of fluid is drained away into lymphatic "sumps" of which there are thousands along the air passages. The alveolar fluid may have bacteriostatic properties. Dust and bacteria which are not eliminated may settle in these "sumps" (rather than being transported through barriers of tissue by "boring" phagocytes) and there initiate pathologic reactions.

The important functions of the mucosa of the air passages are more clearly known, but some of the finer distinctions of cellular structure and function have been disclosed by modern technics such as electron microscopy and fluorescent staining as reported by Rhodin and co-workers (6).

It may be said that normal physiology, among other factors, preserves a protective dampness of the respiratory surfaces. Disturbances which cause superfluous accumulations of fluid (and probably those also which modify its physical and chemical composition) predispose to infection and pneumonia, e.g., the hypostatic pneumonia of heart failure and the obstructive pneumonia developing in the congested and edematous segments distal to a bronchial lesion (7). In postoperative periods, particularly after procedures in the upper abdomen, pneumonia and other difficulties are often related to poor pulmonary ventilation, aggravated perhaps by the recumbent position of the patient (8). Superfluous fluid may accumulate in the air spaces, and this is a medium for the implantation and proliferation of bacteria. Prevention and relief of the complications depend largely therefore on the correction of ventilation and bronchial drainage. Thoren (9) has studied means of accomplishing this in patients operated upon for disorders of the gallbladder. Physical therapy, consisting of respiratory and coughing exercises one to two days before operation and four to eight days after, reduced pulmonary changes shown by x-ray examination by more than two-thirds as compared with a group of controls; emphasis is placed upon the benefits to obese and elderly patients.

RESPIRATION AND ITS DISTURBANCES IN THE NEWBORN

Cook *et al.* (10) measured respiration of infants, weighing 2.5 kg., in the first week of life: the minute volume of ventilation averaged 498 ml., the tidal volume 15 ml., and the alveolar ventilation 355 ml. The commonest reasons for an infant's failure to breathe, according to Potter (11), are the cytotoxic states of the respiratory center caused by anoxia, by depressant drugs, or by other toxic states in the mother; plugging of the bronchi with mucus is rarely a cause. "All infants who do not breathe are ill." Schaffer *et al.* (12) estimate that pneumonia is the sole cause of death in 6 to 9 per cent of all stillborn and newborn infants; it is questionable whether this rate can be influenced by giving antibiotics to mothers whose membranes have been ruptured or whose labor is prolonged.

Pulmonary Hyaline-Like Membrane

This is a change in the lungs of infants who, when affected, usually die within 48 hr. of birth (13); it has not been observed in stillborns or in those living less than one hour (14). Diffuse mottling, becoming confluent, may appear in the roentgenogram (15). Pathologically it is characterized by an eosinophilic membrane lining alveoli and alveolar ducts. The incidence is said to have increased in recent years as a result perhaps of the administration of high concentrations of oxygen to newborns in incubators. It occurred in 4.7 per 1000 live births (over 1000 gm.) without significant atelectasis and in 2.4 per cent with at least 70 per cent atelectasis in the series of Latham and co-authors (16); prematurity, multiple pregnancy, caesarean section, and diabetes in the mother were associated with more than average frequency.

Gitlin & Craig (17) found the membrane containing a large amount of fibrin, originating apparently in effusions from the pulmonary circulation. While the theory of formation of the membrane from aspirated amniotic fluid alone has been generally discarded in recent years, these authors concede the possibility that thromboplastin in this fluid may aid in the conversion of fibrinogen to fibrin. Experimental support of the plasma transudation theory is supplied by Hadders & Dirken (18), who produced the membrane by injecting rabbit serum into the lungs of rats. Lynch (19, 20), on the other hand, interprets his evidence to mean that the membrane represents a dried and concentrated secretion of the respiratory bronchioles and alveolar ducts, containing a hemoglobin-like compound. It is suggested, on the basis of finding iron in the pulmonary hyaline membrane of an adult with mitral stenosis, that pulmonary hemosiderosis in rheumatic heart disease may result from repeated episodes of hyaline membrane. A dry atmosphere seems to favor its development in infants, and a high humidity is considered to be indicated as a part of prophylaxis and treatment.

PULMONARY HEMOSIDEROSIS

Recent studies suggest this condition may result from any of a number of causes. There is a rare idiopathic variety in children and another secondary to mitral stenosis in older people. In the former there are periodic attacks of dyspnea and cyanosis, pulmonary hemorrhage, and development of iron deficiency anemia without generalized hemolysis. Pathologically, according to Fleischner & Berenberg (21), there are massive diapedeses of red blood cells from the pulmonary capillaries, which are dilated and tortuous with thickening of the alveolar basement membrane, increased connective tissue, and edema. The elastica of the lung is grossly deficient and, from some areas, absent. Hemosiderin is found in the alveolar spaces and epithelium, in walls of small and medium sized pulmonary vessels, and in lymph nodes. There is no nodular accumulation of iron or fibrosis.

However, in the form accompanying rheumatic heart disease, chiefly in the third and fourth decades of life, Esposito (22) reports the salient patho-

logic finding to be a well-demarcated nodule of agglomerated, pigmented macrophages produced by repeated hemorrhages. He found the condition at autopsy in 28 of 100 cases of severe heart disease, while Taylor & Strong (23) record an incidence of 42 per cent in patients dying with advanced mitral stenosis. Released hemosiderin may impregnate the elastica and capillary membrane, the result of small hemorrhages attributable to chronic congestion and pulmonary hypertension. Esposito found localized fibrosis, apparently induced by hemosiderin, but Taylor & Strong were not impressed with this. Clinically the pulmonary changes are considered benign. Radiologically, many have observed miliary densities, simulating tuberculosis, pneumoconiosis, sarcoidosis and metastatic carcinoma. But, in the idiopathic form, Fleishner emphasizes a diffuse cloudiness at first, later perhaps changing into reticular shadows.

Cameron (24) discovered hemosiderosis, resembling that with mitral steonosis, in the autopsies of two patients with bronchiectasis, one a boy of 15 and the other a man of 51 who also had pneumoconiosis; there was a foreign body reaction with giant cells also. The contained iron was shown to be ferrous; calcium and phosphates were also present in the lesions.

PULMONARY FIBROSIS AND GRANULOMATOSIS OF UNCERTAIN ETIOLOGY

Sarcoidosis

The recent studies refer in large part to the clinical features and to odd manifestations of the lesions in structures such as the central nervous system, hypophysis, kidney, liver and spleen. The relative frequency of sarcoid lesions in muscle compared with the rarity of tuberculosis there has led to the procurement of specimens of muscle (gastrocnemius; scalene) for diagnostic purposes in some clinics (25), although lymph nodes are obtained, when needed, by most. Mather *et al.* (26) commend the liver biopsy as safe and reliable. They obtained positive histologic evidence in this way in 59 of 93 patients with sarcoidosis, finding no relationship to sensitivity to tuberculin, the level of serum globulin, or to the form of the disease; serial biopsies reflect the evolution, eventually showing residual fibrosis. The predominance of mediastinal or pulmonary manifestations or both was observed by Siltzbach (27) and many others in a majority of cases of sarcoidosis, and the frequency of intrapulmonary adenopathy is noted by Wigh & Montague (28), being 75 per cent in a group of cases with intrathoracic lymph node enlargement compared with 25 per cent in cases of lymphosarcoma and Hodgkin's disease. This adenopathy is most readily detected along the course of the right descending pulmonary artery and was always present in 50 cases of sarcoidosis where the anterior mediastinal nodes were enlarged.

Kveim test.—Performed by the injection of a sarcoidal lymph node suspension into the skin, a positive reaction consists of the development in two to three or more weeks of a small papule which, on section, presents the

cellular morphology of a sarcoid lesion. A good deal of disagreement still exists regarding the specificity of the reaction for sarcoidosis. James & Thomson (29) found it simple, safe and specific for diagnosis and an index of activity and effect of treatment. On the contrary Israel & Sones (30) observed reactions in patients with tuberculosis and negative results in patients with sarcoidosis; they consider the test unreliable. Siltzbach & Ehrlich (31) observed reactions in only 2 of 54 control patients and find the test useful, especially when a suitable biopsy of tissue is not available. In our experience the test has been of uncertain value, and we have placed greater reliance on clinical, roentgenographic and histologic findings.

Cause unknown.—Most students of the subject have veered away from the supposition that this is an atypical form of tuberculosis. There have been vague suggestions recently that sarcoidosis is a hypersensitivity disease (32), that it may be caused by a virus, or that it is a collagen disease. Evidence for serologic hyper-reactivity, using mismatched blood, is reported by Sands *et al.* (33). Epidemiologic studies, based on an analysis of 297 cases among World War II servicemen, lead Gentry, Nitowsky & Michael (34) to the suspicion that sarcoidosis occurs with relatively greater frequency among those born in southeastern United States, especially in rural areas; there is a close association with certain types of soil. As a basis of future investigation they suggest factors of diet, vectors, infectious organisms in the soil, mineral substances (? beryllium), and host resistance. Contrariwise, Carr & Gage (35) did not discover a characteristic geographic distribution among 177 cases. The large number of Negroes in the former series (18 to 1 White) and relation to the place of birth might help to explain the difference in the findings.

Treatment with steroids.—It is often difficult to judge the effects of treatment since half or more of the cases undergo spontaneous remission [Buschmann (36)]. This, it is generally agreed, occurs most often in those with disease limited to the mediastinal nodes and little or none in the pulmonary parenchyma. In these cases, steroid therapy is usually to be avoided unless evidence of progressive involvement becomes manifest. An interesting side light, mentioned by a number of clinicians, is the occasional resolution of pulmonary lesions during pregnancy, followed usually by a recurrence. In cases of presumably recent origin, it has seemed to me that a period of bed rest was beneficial. For cases with more extensive or progressive disease treatment with cortisone and corticotropin has brought about an arrest and resolution; in some this is only temporary and relapses have occurred (37, 38). Fibrosis may progress, and in some may actually be accelerated, during and after steroid therapy. Regardless of the kind of treatment fibrosis is a natural outcome of sarcoidosis and is to be expected probably in the majority of cases. Usually mild, it may progress to a dense alveolar-capillary barrier, interfering with the diffusion of gases, and may eventually lead to right heart failure and death. During steroid therapy a watch is to be kept also for the possible development of tuberculosis. The over-all mortality among cases

of sarcoidosis is estimated by various writers to be as high as 10 per cent. In view of this and the frequency of permanent respiratory impairment it is no longer regarded as a benign disease.

WEGENER'S GRANULOMATOSIS

This unusual, grave and fatal disease has its principal effects in the upper and lower respiratory tracts, at least at the start. Godman & Churg (39) suggest that it is a phenomenon of hypersensitivity and that these structures are the first, most susceptible "shock tissues." Later in the course there is evidence of generalized focal necrotizing vasculitis, nephritis, and granulomata, and death in uremia appears to be common. Necrotizing giant ulcers and granulomata are found in the upper air passages and in the bronchi and lungs; Leggat & Walton (40) mention excavating pulmonary lesions. The nature of the incitant is unknown but is assumed by Godman & Churg probably to be microbial. The close resemblance of certain features leads some to the view that this is a particular form of polyarteritis nodosa. Milner (41) reports a case of this kind in which the initial manifestations were in the upper respiratory tract; these resolved but the patient later died in uremia.

Other Unusual Chronic Bronchopulmonary Disorders

In adults there is a large variety of pulmonary fibroses and associated chronic pulmonary diseases which, when they first present themselves, are so obscure in origin as to baffle understanding. In some there are vague indications of long duration such as slowly increasing dyspnea, a chronic cough, or malformation of the chest. The possibility of origin in childhood should not be ignored, particularly if the identification of such linkage might lead to finding means of prevention. With the use of antibiotics for respiratory troubles in children, it is probable that some will survive who formerly would have died early and that these may bear damage in the respiratory tract which will be a handicap in the after years. The lengthening span of life may then bring this damage to the fore. For these reasons, among others, it is interesting to consider some recent studies of the hazards of childhood when the odd and bizarre may add their number to the commonplace.

In fibrocystic disease of the pancreas.—The broncho-pulmonary manifestations of this condition, which di Sant'Agnese (42) characterizes as a generalized disease of the exocrine glands, are almost always present; in his group of 325 cases there were 145 deaths, 130 of which were attributed to the pulmonary involvement. The majority of chronic nontuberculous diseases of the lungs in Caucasian children are related to this condition. Initially acute infection stimulates a hypersecretion of mucus (latterly spoken of by some as "mucoviscidosis"), and this results in varying and recurring episodes of bronchial obstruction with infection which eventually is more

or less destructive of tissue; organizing bronchopneumonia may follow. The plan of treatment in these cases, in addition to measures for the underlying pancreatic disease, includes the use of antibiotics against the infection which basically is attributable to *Micrococcus pyogenes* var. *aureus*. Prophylactically, broad spectrum antibiotics are often indicated continuously for months or years. The benefit sought may be lost because of the invasion by drug resistant strains of the organism.

In familial dysautonomia.—Here, according to Moloshok & Mosely (43), disordered function referable to a congenital disturbance of the nervous system in children produces a syndrome of bronchial hypersecretion and its sequels, practically identical with that associated with fibrocystic disease of the pancreas.

Pulmonary tuberous sclerosis.—This congenital condition, associated with anomalies in the brain and elsewhere, becomes manifest usually in the third decade of life, especially in women, because of the development of breathlessness and possible hemoptysis (44). Then it is usually fatal within five years. Rarely the only site of lesions is in the lungs. Roentgenographically, as in some other chronic diseases, the pulmonary shadows are miliary, reticular and honeycombed. On section the lungs show tiny cysts, some with bronchial connections, in a matrix of muscle, fibrosis and vessels.

Pulmonary fibrosis with dermatomyositis.—Mills & Mathews (45) report an apparently unique example in a woman of 52. They suggest a logical grouping of this with other collagen diseases, possibly of common etiology. In scleroderma the occurrence of associated pulmonary fibrosis has been observed more often.

Pathology.—Heppleston (46), on the basis of his study of 66 cases of "honeycomb" lung, views this as an acquired form of cystic disease which may be focal, irregular or diffuse. The essential change is the obliteration by fibrosis or granulomata of small bronchioles with dilatation of neighboring healthy branches to form cysts; a valvular mechanism may then cause the cysts to enlarge. The fibrosis may arise from organizing bronchopneumonia and areas of pulmonary collapse, or from the granulomata of eosinophilic granuloma, sarcoidosis, beryllium disease, or tuberculosis after specific therapy. Muscular hypertrophy is a common feature. The spaces may be lined with simple epithelium, which sometimes proliferates excessively and gives an appearance of adenomatosis. There may be squamous metaplasia, but this does not go on to malignancy. Another outcome of chronic inflammation without much fibrosis is smooth muscle hyperplasia of the lung, the "muscle cirrhosis" of von Buhl. Rubenstein *et al.* (47) think this may be a functional response.

PULMONARY MICROLITHIASIS

The cause of this peculiar and unusual disease, which produces a unique roentgenographic picture of fine nodular and reticular shadows having the

density of calcium and which may lead to progressive impairment of respiratory function, is unknown. However, several recent reports contribute information suggesting hypotheses. All mention the characteristic concretions within the alveolar spaces, the so-called corpora amylacea. Badger *et al.* (48) found stones also in both kidneys of their patient who died, and they suggest a metabolic disturbance as the cause. The ash from a section of a lung revealed phosphorus pentoxide, 38.8 per cent, calcium oxide, 51.8 per cent, and ferric oxide, 0.1 per cent. A biopsy in the case of Kent and co-workers (49) showed concretions 0.02 to 0.3 mm. in diameter; amyloid stains were negative, and the bodies contained doubly refractile lipides and were heavily calcified. They suggest that the condition may result from an unusual exudative response to various insults. Sato (50) reports the finding of cases in three Japanese sisters, aged 6, 10, and 19 years, respectively, suggesting an hereditary factor. Determinations in two did not show abnormalities of the serum calcium or phosphatase. Analysis of the ash of a biopsy specimen of the lung obtained from one patient showed SiO_2, 0.93 per cent, P_2O_5, 41.19 per cent, K_2O, 2.02 per cent, CaO, 48.20 per cent, MgO, 2.84 per cent. A peculiar feature of this condition is the scantiness or absence of fibrosis which is not consistent with the presence of irritants of a bacterial, chemical, or other kind. It is more suggestive of the accumulation of some neutral matter which, when it fails to be absorbed or expelled, becomes infiltrated with concentrated inorganic chemicals as described.

PNEUMOCONIOSES

A notable recent contribution to the understanding of occupational diseases of the chest is the publication of the *Transactions of the McIntyre-Saranac Conference* (51) held at Saranac Lake in 1955. This contains more than 50 articles, the majority referring to original investigations. The measures introduced by industry to suppress dust to which workers may be exposed, automatic machinery reducing the number of employees, better medical supervision in plants, public health safeguards against tuberculosis, and changing economic conditions all seem to have helped in reducing disability and death from silicosis. Nevertheless, it is still a serious problem.

Functional impairments.—Wright (52) distinguishes the derangements in silicosis from those observed in asbestosis. In the discrete nodular phase of the former, dysfunction seldom occurs; in the later conglomerate phase the findings are those of diffuse obstructive emphysema. He emphasizes the lack of close correlation between roentgenographic appearances of the lungs and respiratory function. Rossier *et al.* (53) agree, noting that ventilatory deficiencies early in the course of the disease may be explained by complicating bronchitis and emphysema. Gilson & Hugh-Jones (54) consider age of the patient to be more important than the roentgenographic degree of simple pneumoconiosis in judging disability. While disability in the later years of life usually comes from an accumulation of different changes, including those caused by infections, it is rather clear in most cases that

pneumoconiosis, when present, is a contributory factor. The association of bronchitis, adding so often to the breathing difficulties, is observed most commonly among older men. The studies of Gilson & Hugh-Jones, conducted among coal workers, revealed more emphysema among miners with demonstrable pneumoconiosis than among those without. Breathlessness on exertion is attributable to a diminution of maximum ventilatory capacity rather than increased ventilation required for exercise. Severe disability among these workers is most often associated with a conglomeration of the nodular lesions, called progressive massive fibrosis by the British. This change appears most often to be the result of infection, especially tuberculous. Cochrane (55) thinks that a little coal dust in the lungs may protect against progressive tuberculosis whereas large accumulations may have the opposite effect.

There is still some controversy regarding the noxious effects of coal dust alone. Among the miners pathologic examinations have disclosed accumulations of coal dust about the respiratory bronchioles associated with "perifocal emphysema" but little or no fibrosis. In others the admixture of other dusts, especially silica, may cause more complicated lesions. In experimental work with mice Legerlotz (56), using injections of various dusts into the peritoneum of mice, found that the addition of very small amounts of quartz (0.5 to 1.5 per cent) to mixed dust rich in carbon, modifies the tissue reaction and produces "silicosis-like" nodules. In any event it is recognized that coal workers may suffer from the effects of their occupational exposure (57).

Wright identifies the abnormality of function in patients with asbestosis as a result of impaired oxygen transfer to the blood rather than impaired breathing ability and ventilation.

Modified pneumoconiosis in coal miners with rheumatoid arthritis.—These lesions (Caplan's syndrome) which cast circumscribed rounded opacities in the roentgenogram were studied in the specimens of lungs from 16 Welsh coal miners by Gough *et al.* (58). The nodules represent a modified form of pneumoconiosis and contain necrotic collagen and dust. Tuberculosis was present in 40 per cent, but there was also a nonspecific inflammation believed to be on a rheumatoid basis.

Protective effects of aluminum and other agents against silicosis.—The value of inhaled aluminum in a powdered metallic or other form has been a matter of disagreement. Osmond (59) found that the inhalation of 1650 mg. powered Al by each employee in a foundary per year was related to a decreased incidence of silicosis and to improved function among men who had some respiratory incapacity. Dworski (60) using colloidal aluminum hydroxide or powdered aluminum hydrate in animals was able specifically to inhibit the characteristic silicotic reaction to quartz for more than a year. The injection of aluminum caused healing of immature tissue reactions, but fibrous nodules did not disappear. Schepers and co-workers (61) found that calcined gypsum dust mixed with quartz dust gave some protection to

guinea pigs against the usual harmful effects of the latter; but this was only temporary and was no longer operative when the exposures ceased and the gypsum disappeared from the lungs.

Beryllium Poisoning

A case register has been set up at the Massachusetts General Hospital under the supervision of Hardy (62). In the chronic form of pulmonary disease attributable to beryllium poisoning (which resembles sarcoidosis) she has observed benefit from the administration of corticotropin or cortisone or both in long-term courses. Acute beryllium pneumonitis has been prevented by observing the recommendation of the Atomic Energy Commission in establishing the maximum allowable concentration of 25 μg. of beryllium per cubic meter of air. A maximum of 2 μg. per cubic meter has been recommended for chronic exposure, but the reliability of this must await the test of time since the effects may be delayed five years or longer. Theodos *et al.* (63) report a chronic pulmonary case developing eight years after the exposure.

Other Metallic Oxides

In addition to the problem of beryllium an awareness of possible harm to the bronchi and lungs from the inhalation of metallic oxides in the form of fumes or dusts has been growing (64); these include oxides of manganese, vanadium, osmium and tantalum. The effects are usually of an acute inflammatory character and pneumonia has also been observed. In the ash from the burning of crude oil the content of V_2O_5 may be high as 65 per cent, according to McTurk *et al.* (65), and this, of course, may be inhaled by boiler cleaners. The mild chronic inflammation of the upper respiratory tract as a result of vanadium may simulate that attributable to infections. Determinations of vanadium in the urine give the best evidence of recent exposure.

A perusal of the *Transactions of the McIntyre-Saranac Conference* impresses one with the numerous possible pulmonary effects of occupational hazards in general and the need of continuing research in this field. Among other substances the reports deal with cobalt, tungsten, talc, glass wool and rare earths.

Pulmonary Effects of Ozone

The toxic effects of ozone have received the attention of Mittler *et al.* (66). The hazard is encountered, for instance, in pressurized aircraft at an altitude of 65,000 ft., when the occupants are exposed to four p.p.m., by weight, of ozone. Animals poisoned by O_3 were quiet and dozing in 15 min.; after 2 hr. the breathing was labored and rapid, and some animals died. The lungs showed extensive hemorrhages from the capillaries and edema fluid accumulated in the respiratory system. Exposure to O_3 for more than 3 hr. should be limited to three p.p.m. or less.

PULMONARY MYCOSES

Soil as a natural reservoir of pathogenic fungi.—Various studies, including those defining the peculiar geographic distribution of certain mycoses, have suggested that the causative organisms live in the soil. Ajello (67) reports an extensive study of 1215 specimens of soil obtained in the United States and five other countries. From various samples he was able to isolate *Allescheria boydii, Candida albicans, Coccidioides immitis, Cryptococcus neoformans, Histoplasma capsulatum* and *Microsporum gypseum.* Except for the first and last mentioned, these are known to cause disease in man rather often; the frequency of pulmonary involvement is attributable presumably to the ease with which they may be inhaled. The source of *Blastomyces dermatitidis* has not been found, and it has never been cultured from the soil (68).

Histoplasmosis

The geographic distribution of infection with *H. capsulatum,* determined by skin tests of 68,452 young adults who were lifetime residents of single counties in the United States, is reported by Manos *et al.* (69). Of the reactors 60 to 90 per cent were from central states; 30 to 60 per cent were included in a surrounding circle up to three hundred miles wide. A number were found toward the West but there were almost none among lifetime residents of the Atlantic and Pacific coastal areas. Soils from places where chickens lived and other avian habitats are known to harbor the fungus. It was found more often in the soil from chicken houses than from yards (67); chickens, however, are not carriers, and they are difficult to infect experimentally (70). Evidence is presented by Zeidberg, Ajello & Webster (71) to suggest this fungus may thrive best in acid soils. Emmons (72), by obtaining cultures from 4664 apparently healthy animals in Loudoun County, Virginia, found the fungus rather commonly in dogs and cats, and less often in rats, opossums, skunks, house mice, foxes and woodchucks.

An extensive review of the literature on histoplasmosis is presented by Silverman *et al.* (73); and Emmons (74) writes from his long and thorough experience. For diagnosis of pulmonary cases he recommends the inoculation of mice with the patient's sputum. The animals are killed in four weeks, and the organs are used to seed Sabouraud's agar or other media with blood; growth is better favored by incubation at 30°C. than at 37°. The infection is not transmitted from man to man, nor from mouse to mouse. Identification of the fungus in tissue sections, even with special staining, may be difficult and unreliable.

Histoplasma infection usually does not lead to manifest disease. Symptomatic, invasive, destructive and generalized forms have been observed most often among infants and to a lesser degree among elderly men. It is identified more frequently now as a complication of other debilitating disease, such as Hodgkin's. The close resemblance of the chronic cavitary pulmonary form to tuberculosis has led to the discovery of a number of cases of the former in

sanatoriums by Furcolow & Brasher (75). White (76) also dwells on the simulation of the one disease by the other during the chronic phases.

In treatment the results of trials of various chemical and antibiotic drugs have generally been negative or dubious and temporary. Nejedly & Baker (77) report the healing of a case of ulceration of the hard palate and gingiva under treatment with 2-hydroxystilbamidine, but there are no reports of comparable benefit to visceral lesions.

Coccidioidomycosis

Infection with *C. immitis* is transmitted to man from the soil (most often desert dust) where the organism lives in its saprophytic mycelial phase; similarly infections have occurred from laboratory cultures. In diseased human tissues, the fungus is found in the form of a parasitic spherule (endosporium). The demonstration of mycelial forms on the surface of walls of pulmonary cavities in three cases and in the necrotic debris of granulomata in three others is reported by Fiese & co-workers (78); they also claim to be the first to mention the demonstration of mycelia in the sputum of patients (four) with pulmonary cavities. This might be a reason to suspect the possibility of transmission of infection from patients with cavitary disease, but such is not known to occur.

A short review of the course of coccidioidomycosis in 100 hospitalized patients is presented by O'Leary & Curry (79). They mention the occasional spread of the infection from a cavity in the lungs through the bronchi, an event which is rather rare compared with its frequency in tuberculosis; this fact is of value in differential diagnosis. Treatment with antifungal drugs generally has been ineffective although a number show some activity *in vitro* and in early stages of the disease in experimentally infected animals (80). Dihydroxystilbamidine seemed to have some suppressive effect in a few patients treated by Snapper *et al.* (81). The pulmonary lesions usually heal spontaneously and the residuals, with few exceptions, are considered to be bland and innocuous (82). After a review of 750 cases, in 100 of which surgical treatment was used, Cotton *et al.* (83) established criteria for surgical resection based chiefly on the presence and behavior of cavities. They never observed a cavity to close beyond six months after the acute phase of the disease, and wait for this period before advising resection. A persisting cavity may be superinfected by tubercle bacilli or other organisms. I am a little more optimistic that the cavities, at least the smaller ones, may close after six months.

Blastomycosis

A unique, well studied epidemic, the first proved in the United States or Canada, of 10 cases of pulmonary blastomycosis is recorded by Smith and co-workers (68), which, as they advise, should increase alertness for the possibilities in known endemic areas of the Midwest, Ohio River Valley, and southeastern United States. Seven of the cases were in children under 16

years of age, one an infant of five months. In eight the organisms could be seen in the sputum on direct examination, and the examination of gastric washings was also effective for diagnosis. Erythema nodosum, observed in other fungus infections, is reported for the first time in this disease. Stilbamidine and 2-hydroxystilbamidine were used with good effects in treatment. Similar success has been reported by a number of authors.

Other Fungal Infections

An apparently rare case in a child, attributable to *Cryptococcus luteolus*, is reported by Binder *et al.* (84); the scattered pulmonary lesions resolved slowly. This fungus, according to the authors, was isolated from the air by Saito in 1922.

Stewart (85) has worked with nystatin, an antifungal drug obtained from *Streptomyces noursei*, and finds that it inhibits growth and cell division of species of candida and saccharomyces. Bacteria and leucocytes are not affected by doses which are toxic to fungal cells. Resistance to the drug has not been demonstrated. When administered prophylactically with other antibiotics which frequently favor the proliferation of candida in the intestine, vagina, and elsewhere in the body the drug was not wholly effective. Stewart thinks it has some promise of suppressing the infection where it is most troublesome, viz., beneath dentures and on the atrophic mucosae of elderly people, among those in a poor state of nutrition, in uremia and other toxic states, and where candida prevails in the environment.

TUBERCULOSIS

The year's literature on tuberculosis is so extensive and important that a fairly balanced review is most difficult. I shall attempt only to touch upon some contributions which seem to be of basic significance in the problem.

The changing pattern.—Drolet & Lowell (86), on the basis of statistical analyses show that during the seven years, 1947 to 1953, the decline of deaths from tuberculosis has been the most rapid in history; this is credited chiefly to modern treatment since the advent and wide use of specific drugs. The decline has ranged in 30 different countries and Puerto Rico, from 38 per cent in Mexico to 83 per cent in Iceland (64 per cent in the United States). In cases coming to autopsy Terplan & Evander (87) find less involvement of the larynx, tracheobronchial structures, and intestinal tract than in former years. Even before the availability of specific chemotherapy, there was a noticeable diminution of the severity of these complications which we ascribed in part to earlier diagnoses. Now it is observed generally that death from acute forms of the disease can usually be prevented or postponed and, consequently, there is not only a much higher rate of recovery but also a greater number of survivors whose disease has been partly controlled and converted into a chronic form. A large percentage of the latter is seen among elderly men. The intrinsic character of the disease has not changed (88).

The decline in morbidity has been at a much slower pace, and it is estimated that about 100,000 people in the United States are being attacked by the disease each year. The rate of primary infection among children has declined, but at a very uneven rate in different countries. In some [cf. Drolet & Lowell (86)] 85 per cent of the city children react to the tuberculin test by the time they have reached early adolescence; in other communities the rate is 5 per cent or lower.

Immunization

Vaccination with BCG (Bacille Calmette Guérin) has received much attention, and the subject of a recent Scandinavian symposium was "Is mass BCG vaccination still justified in Scandinavia?" (89). In view of the changing picture of tuberculosis Wallgren, who introduced BCG to Sweden in 1927 and was the leader of the symposium, expressed the opinion that the risk of acquiring tuberculosis there is now small and that only a very few of those now vaccinated with BCG are likely to be saved from death from the disease. He believes that BCG is still indicated where there is a serious risk of infection, particularly during adolescence. Other participants expressed varying views but none denied that BCG may occasionally be harmful, especially when it is used in mass campaigns. Minor lesions, such as suppurating lymph nodes and lupoid lesions of the skin, are not rare, and a few fatalities attributed to the vaccine have been recorded. C. E. Palmer, a participant from the United States, indicated that the progress against tuberculosis in this country, equal to that in countries where BCG has been used, has been achieved without mass vaccination. Elimination of infection is the goal and for this, he believes, we need the tuberculin test uninfluenced by sensitization which is artificially created by vaccination. Now that human infection is decreasing in frequency and is so often delayed beyond the years of childhood, the test is considered to be very important for detecting those who may be sources of infection.

The proceedings of a symposium in Denver on tuberculosis in infancy and childhood (90) also include informative discussions of immunization. Dubos stated that the resistance of man to tuberculosis can be increased by vaccinating either with living cultures such as BCG or the vole strain, or with various killed bacillary suspensions, or even with purified soluble extracts of the bacilli. Ström discussed his work with BCG labeled with radioactive phosphorus (P^{32}). By this technique he found the vaccine dispersed beneath the skin of young children, presumably through the lymphatics, within 10 to 15 min. after inoculation. By experiments with guinea pigs he was able to show that bacilli are less rapidly dispersed through the body of a previously vaccinated animal than those of normals, a phenomenon of immunity. He also showed that P^{32} is excreted in the urine within 1 to 2 hr., an indication of destruction of labeled bacilli by the defenses of the body. Irvine reported on the use of BCG and vole vaccine in 50,000 British school children. Vole vaccine is apparently harmless except for an occasional vio-

lent local reaction and can be standardized by passage through the vole, an advantage over BCG which is not pathogenic for any animal.

Chemotherapeutic prophylaxis.—Ferebee & Palmer (91) in experiments with guinea pigs found that isoniazid, administered in drinking water before the animals were infected with tubercle bacilli and continued for only 10 weeks afterwards, prevented mortality from tuberculosis for at least 26 weeks. It also appeared that this treatment had some immunizing effect against subsequent infections comparable to that observed after BCG vaccination. Dubos (92), however, objects to the last conclusion and believes a large-scale trial is not justified on the basis of this evidence. There has been a discussion in various circles of the merits of treating young children with isoniazid, shortly after they first acquire tuberculous infection as determined by the tuberculin test, in order to prevent the later evolution of the disease. An organized study is in progress to ascertain the effects in preventing tuberculous meningitis. Not to be forgotten is the view of many that the enhancement of native resistance against the infection by hygienic living is one of the best preventives, especially against the most prevalent form of the disease, the pulmonary.

Treatment

The literature on chemotherapy is voluminous. It is generally agreed that isoniazid, streptomycin, and para-aminosalicylic acid are the most effective and useful drugs; relatively, when carefully administered, these also have less potential toxicity. Except for the use of isoniazid alone by some clinicians, the general practice is to administer two drugs in simultaneous courses and to continue the chosen regimen for prolonged periods of time, usually from 6 to 18 months after the disease has become arrested in its progress. Systematic studies of the efficacy of various regimens of drugs in large groups of patients have been conducted in Veterans' Administration, Army and Navy hospitals for a number of years; after statistical analysis they have been reported in the Transactions of regular conferences on chemotherapy (93). These are outstanding symposia. They indicate that regimens of isoniazid or para-aminosalicylic acid daily with streptomycin twice weekly are efficacious, the latter pair together being a little better [Tucker (94, 95); Tucker & Livings (96)]. On the basis of carefully conducted trials the British Medical Research Council (97) gives preference to a regimen of streptomycin, 1 gm. daily plus isoniazid, 200 mg. daily, judging solely from the results at three months. Since long-continued courses of therapy are usually indicated it is doubtful whether the comparison of short-term courses can be interpreted very broadly. Middlebrook and his associates (98), in a series of very original and interesting studies, adduce evidence in favor of administering large doses of isoniazid (8 to 16 mg. per kg. body weight per day) with daily doses of streptomycin initially in order better to suppress more highly pathogenic tubercle bacilli and to compensate for varying rates of inactivation of isoniazid in the body. There have been

many regimens reported, some clinicians preferring to give three drugs together; but there is some disagreement as to whether this is superior to the usual two-drug regimens in avoiding or postponing resistance. In cases in which a lasting arrest of the disease cannot be anticipated with some assurance a three-drug regimen may have the disadvantage of exhausting the best available agents; here it seems best to keep one potent drug in reserve.

Resistance of tubercle bacilli to drugs.—Eventually, under almost any regimen of treatment, organisms from the sputum or other sources manifest some resistance to the effects of any of the drugs employed. Bacilli from different lesions may vary in this respect. The manifestation of resistance may be attended by a clinical relapse and may necessitate the substitution of other regimens. The difficulty is anticipated most often in "open" cavitary pulmonary cases.

Resistant strains, especially those tested against isoniazid after treatment with this drug, are often found to be low or lacking in pathogenicity for guinea pigs. This feature has been studied by many. The implications in treatment of finding catalase-negative isoniazid resistant organisms in the sputum have been investigated extensively and interpreted by Russell *et al.* (99). It is rather generally agreed that organisms of varying susceptibility to the drugs usually persist in the tissues during and after treatment and that its duration should take this into account. Russell and his associates hold the rather unusual view that there may be advantages in avoiding too much rest during the early stages of treatment with chemotherapy. They reason that the drugs are most effective against proliferating bacilli, not so much against those which have become dormant. Physical activity of the patient may promote proliferation which, in effect, means that more bacilli would actually be killed by the drugs. Similar views have been held by others who tried tuberculin injections or other agents to make bacilli readier for disposal. This is dubious reasoning for those who believe that good results depend chiefly on the promptness with which the infection is suppressed.

The possible infection of people with drug-resistant strains of tubercle bacilli has caused some concern, but this has not been found to be a frequent occurrence (100). McMurdoch & Grant (101) report the case of a man of 20, who developed tuberculosis after contact with his sister who was under treatment for the disease. His bacilli, cultured before he received chemotherapy, were of low virulence in the guinea pig and were resistant to isoniazid and to streptomycin, the drugs which his sister had been taking. The bacilli obtained from the sister were similarly resistant. It remains to be seen whether low pathogenicity for the guinea pig has the same meaning for man.

A goodly number of drugs have some antituberculous effects, but in the reports of clinical trials none has yet proved to be as useful and effective as those mentioned above, and they are not usually employed in primary treatment.

The place of rest.—Most clinicians and all patients have devoutly wished

for a means to avoid long periods of rest treatment, often in a distant sanatorium, which the disease has been thought to require. Chemotherapy has been seized upon to this end by some, often unwisely and without sufficient consideration of the bacteriology and pathology of the disease. These aspects have been widely studied by a number of investigators who have found in surgically resected specimens of diseased tissue, for instance, remarkable evidences of healing (102). Among these studies one which is notable for its thoroughness is that of the late E. M. Medlar (103). All of these reveal tuberculous residuals, most of them with morphologically intact tubercle bacilli. The bacilli may fail to grow on transference, but it is assumed by many that they may be only temporarily dormant.

A number of organized studies have been undertaken to assess the need of rest along with chemotherapy (104, 105, 106). These are not sufficiently long and thorough to give a final answer. Most clinicians advocate bed rest until the activity of the disease has been well controlled and healing is well under way. This, with needed surgery and other treatment, has been shown to shorten the period of rest treatment considerably.

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PNEUMOCONIOSIS, SILICOSIS, AND THE PHYSICS AND CHEMISTRY OF DUST[1]

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General Characteristics of the Pneumoconioses

Pneumoconiosis is the generic name of a group of lung diseases, caused by the inhalation of dust, which includes coal miners' pneumoconiosis, silicosis, asbestosis, and various other conditions associated with specific dusts. The effects are cumulative and are primarily localized in the lungs, although in advanced cases other organs may become involved. Systemic intoxication, such as results from lead dust, is not included in this review.

The diseases are disabling rather than lethal, though continued exposure to sufficiently large quantities of dust has caused many deaths, and the amount of quartz dust which can produce fatal results is not large. Tuberculosis, bronchitis, emphysema, cardiac failure, and bronchopneumonia are commonly associated with pneumoconiosis.

In 1953 the Pneumoconiosis Medical Panels of Great Britain diagnosed 4,003 new cases in coal miners, over a quarter of which were from South Wales. Other industries contributed 941, of which 354 came from the potteries, 204 from metal manufacturing and sandblasting, and 102 from slate mining (1). Typical results of these diseases to the individual are anxiety, physical weakness, and loss of earning power, such as have been described by Hugh-Jones & Fletcher (2). The community suffers a direct and indirect loss of skilled manpower, and also the cost of compensating victims of pneumoconiosis, which in 1947, the last year before the National Insurance (Industrial Injuries) Act, 1946, came into operation, amounted in South Wales to 2s.11d. per ton of coal produced.

There has been a change in the situation in British coal mines, occasioned on the one hand by an increased awareness of coal miners' pneumoconiosis and, on the other, by the success of measures taken for suppressing dust. South Wales was a bad area and after 1943, when the legal definition of pneumoconiosis was relaxed, the rate of certification rose to a peak figure of 55.6 men per 1,000 employed; by 1947 it had fallen to 30.8. Meanwhile in the rest of the country the corresponding figure for 1947 was only 1.9 men certified per 1,000.

As knowledge of pneumoconiosis spread outwards from the Welsh pits the number of cases in other parts of Britain rose from 597 in 1945 to 3,542 on 1954. The rapid improvement in dust control had its effect, however, and the number of cases in South Wales fell from 5,224 in 1945 to 927 in 1954.

[1] The survey of the literature pertaining to this review was concluded in June, 1956.

In a survey of necropsy material from over a thousand cases of pneumoconiosis which he had examined during a period of 20 years, Gloyne included 394 pottery workers, 302 coal miners, 132 asbestos workers, 103 stonemasons and quarrymen, 102 iron and steel foundrymen, metal grinders and sandblasters of castings, and 172 persons from miscellaneous occupations. Seven hundred and ninety-six of the cases were silicosis, diagnosed by the characteristic nodule which, in minimal cases, could be recognised only microscopically (3).

Inert Dust Pneumoconioses

Coal miners' pneumoconiosis is regarded by some as a disease attributable to coal dust, the presence of silica being unnecessary for its development. The general term, pneumoconiosis, embraces silicosis which is caused specifically by silica dust and differs from the coal miners' disease in that active fibrosis of the lung is a feature of its earliest stages. The coal miner who has not worked in siliceous rock develops fibrosis only after long exposure to dust, when a condition called progressive massive fibrosis is sometimes found; this is believed to be a modified form of tuberculosis in a lung already affected with simple coal miners' pneumoconiosis (4, 5, 6). The gradual accumulation of coal dust in the lungs brings on the simple type, with symptoms only slowly becoming perceptible to the victim and initially difficult to diagnose. Development ceases on the termination of exposure. There is no fibrosis.

Other dusts have been reported as causing inert accumulations in the lungs of a similar nature, with more or less x-ray shadowing which depends on the radio-opacity of the dust as well as on the quantity distributed in the lungs.

These pneumoconioses may be indistinguishable from early silicosis and have been confused with it. For example, Meister (7) describes the effects of emery dust which is not fibrogenic; iron oxide, used as a polish, is found in the lungs of silver finishers (8) and produces marked x-ray changes but little physical disability; collections of iron oxide in the lungs of foundry workers result in dense radiographic shadows, though the dust is not fibrogenic unless accompanied by dust from silica sand, used for sandblasting or in parting powders for mould casting, which is disseminated when castings are fettled (9, 10); tin oxide produces opaque shadows in subjects who have had a long exposure to the dust at some stage of their career, but the disability experienced is quite small (11).

Such accumulations of nonfibrogenic dust in the lungs are sometimes described as benign pneumoconiosis; the term "siderosis" relates to inert deposits of iron dust (12, 13). Examples of benign penumoconiosis are given by Pendergrass & Leopold (14) and Pendergrass & Robert (15).

Some doubt has been cast on the idea that the coal miners' disease comes into this category because dust recovered from the lungs of colliers usually contains a small proportion of quartz. This originates from occlusions and

veins of rock in the coal seam, or from adjacent strata, and is found in men who have worked exclusively with coal. The "hard-header," whose job in coal mines is to tackle the rock work needed to expose the seam, runs a risk of silicosis when the approach to the seam requires work in quartzitic rock.

Since the amount of coal in the lungs of coal getters with long exposures is so large, the net quantity of quartz present may exceed that which would be required to cause pronounced silicosis in workers in siliceous rock. Thus King *et al.* (16) found that in pneumoconiotic colliers' lungs there was an average dust content of 35 gm., of which 0.9 gm. was quartz. This exceeded the amount of quartz (0.7 gm.) found in the lungs of silicotic tin miners containing a total of 4 gm. of dust. Experiments by Jötten & Klosterkötter (17) with animals confirmed British findings that coal dust does not produce fibrosis, while a host of post-mortem examinations of men and animals show that very small amounts of quartz on its own produce fibrotic nodulation. The question is whether the various stages of development of coal miners' pneumoconiosis, culminating in progressive massive fibrosis, are entirely independent of the small (averaging 1:20) quartz content of coal dust, or whether the quartz has an influence, much modified by the large amount of inert dust present, either directly upon lung tissue or upon the chances of infection by tubercle bacilli.

A possible mechanism of interaction, suggested by animal experiments (18, 19), is for the large quantities of coal lodged in a heavily dusted lung to interfere with lymphatic drainage and encourage the accumulation in alveolar tissue of the small proportion of quartz, with the development of diffuse, instead of nodular, fibrosis. Normally, quartz dust which is retained in the lungs finds its way to the peribronchial lymph nodes in which it collects, and the characteristic whorled, fibrous nodules commence to grow. Such nodules are rarely, if ever, found in diseases deriving from other dusts than quartz, provided there is no tuberculosis.

The same problem undoubtedly exists in association with other inert dusts. Thus natural graphite may contain several per cent of free silica; though there is no evidence that graphite alone will cause fibrosis of the lungs, such cases are found in graphite workers along with others in which only simple storage of dust in the lungs has occurred (20, 21, 22).

Parmeggiani (23), describing clinical and radiological investigations of workers exposed to the dust of graphite containing 10 per cent of free silica, claims that the graphite tends to alleviate the sclerosing action of silica; such a conclusion must be regarded as tentative in the absence of accurate data on dust exposure and histological examination of lung lesions. The effect may be one of simple dilution rather than specific inhibition of fibrogenic action.

Dusts Inhibiting Fibrous Growth

Between the dusts producing classical silicosis, with its high rate of fibrous growth in the characteristic whorled nodules, and the inert dusts, carry-

ing only traces of silica which may or may not be of significance, lie others comparatively rich in silica which nevertheless fail to give rise to the classical symptoms culminating in death with a lung dust content of only a few grams.

Haematite iron ore, containing 9 to 12 per cent of free silica, produces very dense shadows in chest x-rays. These, however, are a result of the high x-ray absorption of iron, and there is no stimulation of collagenous fibrosis, which is present only in association with tuberculous infection (24). The suggested explanation is that iron oxide is deposited as a film on the surface of the quartz particles and prevents their fibrotic action (25).

Heffernan (26) described the exposure of makers of ganister bricks to dust containing 84 per cent of silica, the rest being mainly clay; neither silicosis nor a high mortality from tuberculosis existed in this occupation, and he concluded that the nonsiliceous part of the dust interfered with the usual harmful influence of the rest. No figures are given for the exposure to fine dust.

A similar reason may account for the absence of classical silicosis amongst miners in the quartz reef of the Kolar Gold Field. They have been described by Caplan & Burdon (27) as suffering from pneumoconiosis and showing x-ray shadows quite like those seen in South Wales coal miners. The average quartz content of the dust was 13 per cent, but the disease was very different from classical silicosis, fibrotic changes being absent except when the lungs were infected with tubercle. Ray *et al.* (28) conclude that some of the airborne dust may not have contained much free silica, but that the presence of 10 to 11 per cent Al_2O_3 in the reef was probably significant as it could depress the activity of quartz by surface action; presumably the aluminium was present as silicate. King (128) had observed that the admixture of shale and other dusts with powdered quartz caused a decrease in its solubility.

Amorphous Silicates

Passing on from the above pneumoconioses attributable to inert dusts and to silica mechanically mixed with inert dusts, some constituent of which may inhibit or modify the fibrogenic nature of the silica, we come to cases of exposure to siliceous dusts in which the SiO_2 group is in chemical combination again, possibly, with inhibiting groupings. There is an enormous number of mineral silicates and though many cases of pneumoconiosis have been reported amongst men who work with them, the circumstances are too complex and varied to permit of easy classification; the chief difficulties are that rocks and clays are mixtures which frequently contain free silica along with the silicates, and that tuberculous infection often complicates the clinical picture, especially in cases resulting from long exposure to dust.

Clays, which are the decomposition products of crystalline silicates in rock, are aggregates of extremely fine particles and are used in various industries. Physically they are allied to the crystalline silicates as colloidal silica is to quartz. When they contain free silica it may be present in crystalline or colloidal form.

China clay, or kaolin, is a degradation product of granite and consists of up to 25 per cent of free silica mixed with hydrated aluminium silicate and traces of other elements. A post-mortem examination of a man who had long been exposed to ball clay dust has been described by Thomas (29), who found silicotic nodules which were less whorled than is typical and had taken a very long time to develop; another case, also of long exposure, is given by Bastenier (30). A survey of 31 pottery workers by Chiappa & Ferri (31) disclosed only a relatively benign silicosis. The exposure of rats to the dust by intratracheal injection of saline suspension by King *et al.* (32) revealed only phagocytosis with no fibrosis within periods of 60 to 161 days. The free silica content of the kaolin was not determined, but the silica solubility was very low. It seems that kaolin is definitely not responsible for a fibrous silicosis, like quartz, and that cases in which fibrosis has been observed are a result of tuberculous involvement (30, 33) of lungs heavily charged with dust, or to the presence of quartz with its action modified by the kaolin which does not, however, inhibit the growth of fibrous nodules.

The comparative freedom from silicosis of men in the brick and tile industry, handling china clays and fireclays containing free silica, is commented on by Uytdenhoef (34). They inhaled dust containing 11 to 46 per cent of free silica in concentrations up to 700 particles per cc. He suggests that the concentrations might have been below the danger level or that the aluminium silicates had an inhibitory effect. Size-selective sampling with determination of free silica in the respirable fraction should have been employed.

Deaner (35) describes silicosis in fireclay miners with histological examination of one case. The man had worked for 23 years as a fireclay miner in a colliery where the clay was adjacent to the coal seam. The clay was mainly aluminium silicate with only traces of iron, calcium, potassium, and sodium, but it contained a substantial amount of free silica. Laminated fibrous nodules of classical silicosis were present in the lungs. The occurrence of silicotic nodulation in this case and that of Thomas (29) argues against a specific inhibitory action by colloidal aluminium silicate which appears, on its own, to cause an inert dust type of pneumoconiosis.

Fuller's earth, another clay, is a hydrated alumino silicate containing iron. It has been reported as causing pneumoconiosis (36, 37, 38). Quartz was present in these cases, but the disease differed from classical silicosis and and took longer to develop. The dust contains 50 to 60 per cent of combined silica, i.e., SiO_2 in silicates.

A number of cases of silicosis, diagnosed by chest x-rays, are described by Rombola & Guardascione (39) in the bentonite industry; there had been very heavy exposure to dust. This clay is mainly montmorillonite; it contains a trace of quartz along with 32 per cent of amorphous silica plus beta-cristobalite. There were no post-mortem findings to indicate whether the disease was correctly described as silicosis, exemplified by the classical nodulation, or whether there was diffuse fibrosis and to what extent. The maximum exposure was seven years. A dust containing 32 per cent of free

crystalline silica, inhaled in the concentration and particle size described, would normally have been lethal in this time.

Peretti & Occella (40) suggest that the fibrogenic action of quartz is enhanced in the presence of certain clay hydrosilicates. There appears to be no evidence for this statement, either on physical, chemical or clinical grounds. The rapid onset of silicosis leading to death within a few years, which was common in the days before precautions were taken, among men quarrying sandstone, shaping it, or grinding upon dry sandstone wheels, has no parallel in the exposure to silicates in clay or crystalline form, even when an appreciable amount of free quartz is present. The evidence is towards a diminution of the activity of quartz, attributable rather to the presence of an inert diluent than to specific inhibitory action. Pneumoconioses caused by inhaling dust from clays are essentially slow in developing, even under quite dusty conditions.

Occella (41) has analysed many industrial clays and has found free quartz present in proportions up to 50 per cent. This figure did not always provide a good index of the hazard likely to be attributable to the material, because a low concentration of quartz was often associated with a high proportion in the finer particles, which alone were small enough to be retained in the lungs.

A survey of the cement, clay, and pottery industries by Sayers *et al.* (42) showed the main hazards to be the well-known ones attributable to silica and lead. A study by Parmeggiani (43), based on mass radiography of workers in the cement industry, proved that the highest incidence of pneumoconiosis was amongst those employed in mines and quarries where raw materials were obtained and cement dust was absent. Few workers in the factory where cement was made showed more than slight lung shadows. This was confirmed by Giulani & Belli (44), who x-rayed 180 people working in a cement factory and found no cases of silicosis, although 20 per cent of them gave indications of inert dust deposits. Upper respiratory disturbances were prevalent confirming that industrial hygiene practice should not be restricted to eliminating fine, respirable dust. Russell (45), also, observed the tendency of cement dust to cause bronchitis but found no encouragement of tuberculosis and only slight pneumoconiosis.

Experiments in which rats inhaled dust of Portland cement containing less than 1 per cent of free silica revealed no fibrotic changes (46). Miller & Sayers classed Portland cement as an absorptive dust when tested by peritoneal injection, since the initial lesion dispersed and the dust disappeared (103).

Nonfibrous Crystalline Silicates

Passing on to the crystalline silicates, several papers have been published on exposure to dust of the felspars. These comprise two similar groups of hydrous alumino-silicates of alkalis and alkaline earths crystallising isomorphously in monoclinic and triclinic forms.

Experimenting by the intratracheal injection into rats of dust suspensions in saline, Mohanty *et al.* (47) found that felspar was very much less fibrogenic than quartz. Policard & Collet (48) confirmed this work; they compared three kinds of felspar and obtained varying amounts of fibrosis, increasing with time but always less intense than was produced by silica. Their technique was the intraperitoneal injection of saline suspensions. Klosterkötter & Jötten (49), using intratracheal injection, found only slight fibrosis from a potash felspar; hornblende, another complex crystalline silicate, gave none.

Rotter & Gärtner (50), describing a fatal human case with extensive tuberculosis, state that the nodules were not like those of silicosis, being more widely disseminated; there was also less increase in reticular fibres and collagenous tissue. The dust inhaled by the victim contained 38 to 45 per cent of quartz with many particles smaller than 5 μ; they supposed the aluminium, potassium, sodium, and calcium ions, which would leach out into solution, had exerted a neutralizing effect.

Granite consists of about two-thirds felspar with one-third quartz and mica; it contains small amounts of iron, magnesium, calcium, etc. Silicosis with nodulation is produced in men exposed to the dust, but there is more tendency to diffuse fibrosis than with straightforward silicosis. The condition is progressive and associated with tuberculosis, which causes the deaths, but a much longer exposure is required than would be the case with pure quartz dust. These conclusions were reached following exhaustive studies of granite workers in Vermont (51, 52).

A survey of 355 stonemasons in Australia who worked on sandstone (90 per cent free silica), granite (30 per cent free silica), and limestone (non-siliceous) revealed seven cases of silicosis in sandstone workers and one in a granite mason. Seventy-nine cases of moderate, diffuse fibrosis were seen, without incapacity, and the amount of lung damage was judged to be proportional to the free silica content of the stone worked (53).

In France exposures of up to seven years to very high concentrations of granite dust, produced while tunnelling through rock containing 18.4 per cent of free silica, failed to cause silicosis (54). Surveys of the Austrian and German granite industries led Röhrl to conclude that compensatable silicosis was caused only after breathing the dust for many years (55). Experimenting with rats by intratracheal injection of saline suspensions of Cornish granite dust, King *et al.* produced focal nodulation in 100 days. The nodules, however, contained only a tangled reticulin network without collagen and did not progress up to 250 days (56).

Kaolin is derived from granite, and reviewing the evidence relating to kaolin, felspar, and granite together, it is fairly clear that these substances produce silicosis when inhaled as dusts by virtue of their content of free silica. It is also very doubtful if any inhibitory action can be ascribed to these minerals in respect of the fibrogenic property of free silica. There is no doubt that fibrous nodulation in human lungs results from the inhalation of the dusts and that the aluminium silicate which they contain does not prevent

it. Some degree of modification of the nodule, the presence of diffuse fibrosis, and the long duration of exposure required all seem factors which can be accounted for by the dilution of active siliceous dust by inert silicates.

A method of assessing the silicosis risk attributable to dust made from a particular rock was proposed by Landwehr (57). A danger figure was attributed to each mineral constituent of the rock and multiplied by the weight present. The products for all the constituents were then summed, and the total was multiplied by a fraction representing the percentage of fine dust generated by drilling. No account was taken of constituents which could suppress fibrogenic activity, nor of the fact that the "danger" of a mineral might be a result solely of its quartz content; felspar, for example, was rated as 70 per cent as dangerous as quartz. A scheme of this nature suffers from the limitation that the effects of quartz are different from those of other rocks, which makes it rather misleading to classify them together. Landwehr's treatise contains useful information about a number of rocks.

The olivines, orthorhombic silicates of magnesium, and ferrous iron appear to provoke little fibrosis in the lungs. Experiments on rats by King *et al.* (58), using intratracheal injection of saline suspensions, revealed phagocytosis with the alveolar walls thickened because of congestion of the lymphatics by dust containing macrophages. Slight fibrosis was present in the alveolar walls, but there was no organized focal nodulation. These minerals are used as a substitute for siliceous sand in various industries and have contributed to the decline of silicosis.

Sericite, a muscovite or potash mica, is an alteration product of felspar. Some historical interest attaches to sericite because Jones (59) claimed that it was the cause of silicosis. His argument was based upon his discovery in the lungs of silicotic miners of large numbers of fine needles of sericite under 2 μ in length; quartz particles were also present but in numbers subordinate to sericite. Evidence against this theory was put forward (60 to 63), and both Lemon & Higgins (64) and King *et al.* (65) found that sericite produced a minimal tissue response when injected into rats' lungs; appreciable fibrosis was evoked if the dust was treated with hydrochloric acid before injection, though anomalies between solubility and pathological effect were observed. Landwehr (66) claimed sericite to be harmless on its own but to act as a catalyst and to enhance the danger of quartz; his evidence for this statement is not clear. Support for Landwehr's hypothesis is found in papers by Weiland (67) and by Hurlbut & Beyer (68). The experiments of the former, on guinea pigs, seem to have been confused by intercurrent disease. The latter compare two foundries, one with many cases of silicosis and the other with none. While associating the disease with the sericite content of a parting powder used in the bad foundry, and even commenting on the fact that the castings which it turned out possessed a finer finish than those from the other, they entirely fail to record any details of the fettling processes or measurements of dust concentrations during this operation, which was obviously prosecuted more vigorously in the foundry with the high incidence of

disease. The fettling of castings is the principal cause of silicosis in foundries. It is difficult to credit the theory of Hass (69) that sericite is formed out of quartz within the lungs.

An examination of men working with mica and pegmatite (a mixture of quartz and felspar with some mica) by Dreessen *et al.* (70) revealed true silicosis only amongst men exposed to quartz, though effects were seen that could be ascribed to mica dust. Silicosis has been reported in the Bihar mica mines, but this was probably a result of free silica which was present in rock drillings to an extent between 11 and 67 per cent (71).

Sericite and mica frequently accompany silica in silicotic lungs and other dusts in pneumoconiotic lungs, and it is improbable that any appreciable inhibitory action can be ascribed to them. This view is supported by experience in the slate industry where the danger of the dust is probably attributable to the silica content and is not greatly influenced by associated sericite and mica. The first work on exposure to slate dust in Wales, where the silica content is high (35 per cent) and there is a long history of tuberculosis, was carried out by Wade (72). Silicosis was detected in Australian slate quarries where the free quartz content was 33 per cent (73). In France, however, workers in slate which had a free silica content of only 7 per cent, the rest being largely sericite, showed few signs of respiratory impairment (74). Italian slate also contains a low percentage of quartz, ranging from 2.8 to 8.6 per cent. X-ray photographs of personnel engaged in working Ligurian slate revealed initial signs of pneumoconiosis after 10 to 15 years' employment; silicosis and tuberculosis existed only in men who had retired (75). The diseases had thus required a full working lifetime for their development.

The suggestion that micaceous minerals are liable to cause pneumoconiosis because the particles are flat lamellae does not seem to be borne out by an exaggerated incidence of disease or by a particularly rapid rate of development of disease amongst persons exposed to mica dust. There is certainly no gross effect comparable with the vicious attack from crystalline quartz dust. This suggestion has, however, been made by Landwehr & Bruckmann (76) on the basis of a lack of quartz and an excess of mica and talc platelets in lung sections seen under the microscope. Their result may be accounted for by the small difference between the refractive indices of quartz and Canada balsam which makes the identification of small quartz particles in Canada balsam mounts a difficult matter. Any estimate by visual microscopy of the lung content of dust in particles of the order of 1 μ in size must be subject to considerable uncertainty.

Fibrous Crystalline Silicates

Many silicates crystallise in fibrous form, both as short spicules and in longer fibres; the latter may be either brittle or else silky and flexible, like asbestos, the fibres of which also possess the property of cleaving longitudinally an indefinite number of times.

Sillimanite, an anhydrous aluminium silicate used for special purposes in

the pottery industry, crystallises in hard acicular crystals which do not cleave but are readily ground to powder. Middleton (77) stated on limited evidence that the dust did not appear to be highly dangerous, but it was later held responsible for lung fibrosis, including nodulation, in men engaged in making artificial corundum by heating bauxite and kaolin in an electrical furnace (78, 79).

When rabbits were exposed to airborne sillimanite dust, fibrosis of the lungs with some nodulation was observed (80). Other reports of bauxite fume pneumoconiosis suggest that it is caused by the inhalation of extremely high concentrations of colloidal silica aerosol and that the presence of sillimanite in the fume is incidental. The end result, in these cases, was diffuse, interstitial fibrosis without nodulation, deriving from interference with the koniophage clearance mechanism by the large quantity of dust present in the lungs and the high solubility of colloidal particles of silica (81 to 84). King *et al.* (85), however, have produced a dense, collagenous fibrosis in the lungs of rats by administering large quantities of colloidal alumina (Al_2O_3).

Sepiolite, or meerschaum, a light hydrated magnesium silicate resembling cuttle-fish bone and containing both fibrous crystals and amorphous material, has been cited in one case as a cause of "silicatosis" (86); the x-ray pictures show diffuse shadowing.

The association of the shape of inhaled dust particles with disease is particularly interesting in the case of talc, a hydrated magnesium silicate forming monoclinic crystals which are soft and cleave into small scales and spicules.

Dreessen & Dallavalle found that Georgia talc, a hydrous magnesium silicate containing 20 to 30 per cent of dolomite and 10 per cent of tremolite, was more injurious than tremolite talc (87, 88), though the damage caused was in no way comparable with that attributable to silica dust. The Georgia talc contained many fibrous splinters and aggregates and was composed of hydrous magnesium silicate. Tremolite is a hydrous calcium magnesium silicate which occurs both as slender, blade-like prisms and as silky fibres.

Hogue & Mallette (89), after examining rubber workers exposed to pure talc containing neither fibrous varieties nor free silica, decided that this substance did not produce pathological changes in the lungs, but emphasized that the term "talc" was used commercially in a wide sense to include tremolite, pyrophyllite, and even quartz. Massive lung shadowing in miners of pyrophyllite, a hydrated aluminium silicate similar to talc and occurring in foliated, lamellar and somewhat fibrous masses, was observed by Eason *et al.* (90), but the dust contained from 25 to 35 per cent of free quartz. Porro *et al.* (91) found pneumoconiosis in tremolite workers whose lungs exhibited fibrosis and contained talc bodies resembling asbestos bodies when examined post-mortem. That the fibrous varieties of talc produce a disease analogous to asbestosis, with diffuse fibrosis and asbestos bodies, is confirmed by Siegal *et al.* (92) and by Greenburg (93).

Several other cases of pneumoconiosis, caused by long exposure to talc dust and diagnosed by x-ray as differing from silicosis, have been reported without reference to the shape of the particles (94 to 99). Millman (100) describes a generalized pneumoconiosis from exposure to talcum powder dust which contained less than 0.5 per cent of free silica and was entirely free from the sharp spicules found in the fibrous variety of tremolite talc. There had been 24 years' exposure, a long period, to high dust concentrations, which, with the x-ray reproduced, suggest this to be a case of inert dust pneumoconiosis.

McLaughlin *et al.* (101) made a very thorough examination of the lungs of a worker in a rubber tyre factory who died of rheumatic endocarditis. Although the Norwegian talc dust to which he had been exposed for 33 years contained both platelet and fibrous particles, only the latter, up to 10 μ in length, were recovered from the lungs. Fibrosis was not observed in the root nodes but was scattered throughout the lung in small nodules, more numerous in the lower lobes, which were less compact and lacked the characteristic pattern of silicotic nodules. These nodules were packed with fibrous particles and contained "curious bodies" somewhat similar to those found in cases of asbestosis. There had been no exposure to asbestos.

Rapid development of talc pneumoconiosis, clinically and radiologically similar to silicosis, in workers exposed to very heavy concentrations of dust is described by Alivisatos *et al.* (102). No free silica was present. Dust counts up to 1,925 particles per cc. are quoted; this would not be adequate to account for pronounced x-ray shadowing in periods as short as 16 to 60 months unless a fair proportion of long, fibrous particles was present. No information is given on this point.

Miller & Sayers (103) obtained only an initial foreign body reaction following the intraperitoneal injection of talc (75 per cent fibrous tremolite) and soapstone (65 per cent fibrous tremolite) dust into guinea pigs and, therefore, classed them as inert, while Policard (104), exposing rats to airborne talc dust which contained needle-shaped particles, observed only bronchial reactions and loss of mobility of phagocytes. No fibrosis was found, but the animals were killed off after 20 days which may not have been long enough for it to be recognised. In the human subject talc granulomata of the skin and peritoneum have been described (105 to 109).

Asbestos shares with quartz the capacity for producing rapidly, in a few years, a high degree of fibrosis of the lungs when inhaled as airborne dust. The disease, asbestosis, was first recognised in 1906, and an inquiry into its occurrence was held by the Factory Department of the Home Office in 1928 (110). Its association with tuberculosis is infrequent, compared with silicosis, though this is less marked in England than in the United States and Germany (111). Persons affected with asbestosis have an increased risk of contracting cancer of the lung (112, 113), a tendency which has not been observed with other pneumoconioses (114, 115, 116).

Asbestosis differs from silicosis in additional ways. It does not progress

after exposure to the dust has ceased, and it is characterised by diffuse x-ray shadowing as a result of pulmonary fibrosis which, unlike silicosis, chiefly affects the bases of the lungs, spreading to the middle and upper parts as the disease advances, with the apices usually clear. The laminated, fibrous nodules of silicosis do not grow as a result of the presence of asbestos in the lungs; instead, a diffuse, general fibrosis without calcification is stimulated.

Characteristic asbestos bodies are found in the fibrous tissue, air spaces, and sputum and within macrophages; they consist of asbestos fibres sheathed with iron-containing protein derived from the capillary exudate. They were first observed in the lungs of an asbestos worker in 1927; similar objects have since been found in cases of talc, graphite, carborundum, and coal pneumoconiosis and, possibly, byssinosis. Asbestos bodies may be up to 250 μ long; ultimately, they appear to break up and disperse (117, 118, 119). Injection of asbestos bodies into the peritoneum of guinea pigs failed to provoke the fibrous reaction observed with naked fibres (124); Miller & Sayers (103), however, found asbestos fibres to be inert by a similar technique.

Asbestos fibres produce granulomata of the skin, or asbestos corns (120, 121, 122), which do not contain asbestos bodies. An immediate inflammatory reaction in the peritoneum of mice has been caused by fibres detached accidentally from an asbestos sterilizing filter; talc acted similarly, but glass fibres and mica produced only a slight response with no immediate effect from silica (123), possibly because the particles were too coarse (140 mesh)

Histologically, the characteristic feature of asbestosis is the growth of fibrosis around the fine bronchioles and alveolar ducts, suggesting that asbestos fibres lodge across air channels which are of appropriate diameter and work into the surrounding tissue by virtue of its movement during respiration. This has been supported by the results of many animal experiments at Saranac by L. U. Gardner which have been reported by Vorwald *et al.* (124). These showed that peribronchiolar fibrosis could be produced in guinea pigs, cats, and rats by inhalation of asbestos dust containing fibres around 10 μ in length. No effect was produced in mice. Inhalation of dust almost free from long fibres produced little fibrosis. Further experiments by intratracheal injection of long and short fibre dusts, using various kinds of mineral, were carried out. Using fibres 20 to 50 μ long it was shown that chrysotile, amosite, crocidolite, tremolite, and brucite were active; for some reason anthophyllite was not. Brucite is a fibrous form of magnesium hydroxide which is free from silica. Glass wool, of the same length and 3 μ in diameter, produced no fibrosis. When the dusts were ground before administration, so as to break up the long fibres into pieces 3 μ and less in size, no fibrous reaction was produced by any of them; the only effect observed was a greater or lesser inflammatory reaction with transport by phagocytes to the lymphatics.

The association is with the fibrous habit of the mineral, not with its crystalline form; chrysotile is probably rhombic, amosite is orthorhombic, crocidolite and tremolite are monoclinic, and brucite belongs to the rhombohedral section of the hexagonal systems. Anthophyllite is orthorhombic.

All these minerals, because of an enormously exaggerated rate of crystal growth along a particular axis being encouraged by conditions at the time of their formation, may occur in the form of long fibres which are capable of repeated longitudinal subdivision. It is this growth habit which Vorwald and his colleagues correlate with the power to produce asbestosis; non-cleaving fibres of glass of similar length do not cause the disease. Vorwald and his co-workers clinch their argument with observations following intravenous and intraperitoneal injection.

Quartz particles below 3 μ in size, when injected into the veins, collected in various organs, such as the liver and spleen, and caused the growth of hyalinised fibrotic nodules of characteristic type. The asbestos minerals, ground to particles shorter than 3μ, produced no effect. Intraperitoneal injections of the short fibre dusts caused only the phagocyte reaction commonly excited by inert dusts, with no fibrosis. Long fibre asbestos minerals, including anthophyllite, gave rise to fibrosis.

It is also claimed that direct injection of long asbestos fibres into the spleen did not cause asbestosis because this organ is static, whereas the lung and peritoneum are mobile, which makes the ends of the fibres work into the tissues. Full details of this experiment are lacking from the paper.

Further evidence in favour of mechanical, rather than chemical, action is afforded by their observations that colloidal aluminium hydroxide did not inhibit asbestosis, while King *et al.* (125) found, similarly, that metallic aluminium had no inhibitory effect. These substances prevent fibrosis from quartz (126, 127), although an exception has been mentioned by King (128).

Observations on the disease in humans confirm the existence of a mechanical factor in its origin. A typical case is described by Luton *et al.* (129) of asbestosis in a man who died after 18 years' exposure to concentrations of particles up to 4,000 per cc. containing fibres up to 10 μ in length. There were no localised nodules in the lungs, but a general thickening of the pleura in the lower parts of each lung was evident. Many asbestos bodies were seen, isolated and in groups, and dust particles could be traced, not only in the lungs, but also in the vessels of the liver, kidney, and spleen.

Cartier, describing conditions at the Thetford mines in Canada (130), states that all cases of asbestosis arose from exposures of over 14 years' duration to concentrations exceeding 18 particles per cubic centimetre of chrysotile asbestos fibres, which were dry, partially cleaved, and from 10 to 250 μ long. This concentration is of the order of one-tenth of what would be required to cause silicosis from quartz dust, and less than one-hundredth of the figure associated with an inert dust pneumoconiosis in the same period of exposure. Other dust, consisting mainly of powdered serpentine rock, appeared to be harmless.

Asbestosis from Finnish amphibole, a hard, brittle variety, is described by Noro (131). Fibres and asbestos bodies were found in the lungs of victims, the fibres being mostly 9 μ or less in length and under 1 μ in diameter; a few fibres up to 65 μ long were seen.

Dreessen *et al.* (132), in an exhaustive study of an asbestos textile in-

dustry, where the risk of asbestosis is much greater than in mining, found airborne fibres of a median length ranging from 7 to 163 μ. Asbestosis was diagnosed in many workers and asbestos bodies were found in the lungs. Dreessen and his colleagues comment on the very low dust concentrations which could be held responsible for causing the disease. Concentrations below 180 particles per cubic centimetre, measured with a Konimeter, were suggested as being safe; as no attempt was made to distinguish between fibrous and nonfibrous particles, this does not necessarily conflict with Cartier's figure given above. The asbestos was mainly chrysotile.

Alden and Howell (122) describe corns produced in 99 out of 167 workers with amosite. No asbestosis was detected, but figures for the airborne dust concentration are not included.

These facts do not oppose the theory that asbestosis is caused by fibres penetrating the tissue of the primary lung lobule, in the airways of which they are held up on account of their length; it is also conceivable that easy longitudinal cleavage of the fibres, which results in fraying of the broken ends, may be a necessary physical factor additional to a length exceeding 10 μ. In spite of the failure of aluminium to inhibit fibrous growth, however, the possibility of a specific chemical reaction at the ends of the fibres cannot be excluded.

Asbestos bodies provide visual evidence of chemical action against the invading fibres, probably to render them innocuous, with special activity at fractured ends. The ultimate development of cancer cannot readily be accepted as resulting from mechanical stimulus, or the presence of fibrous tissue, without postulating some accessory cause. The asbestos corn, stimulated by small slivers penetrating the skin of the hand, under which a fibrous response is initiated, seems to be more specific than a foreign body reaction. The handling of glass wool, slag wool, and even glass fabrics causes skin irritation because of the pentration of glass fibres, but corns are not produced, nor is there evidence of pneumoconiosis, although long exposures have not yet been recorded (133, 134, 135). Finally, Kettle (25) injected ground asbestos into subcutaneous connective tissue and produced active lesions, like those attributable to silica.

In considering the reaction of tissue to dust, both the immediate inflammatory reaction, and the long-term, fibrotic effect, have to be differentiated. Regarding the latter, asbestos and talc dusts appear to be selective in respect of both the organ and the species of animal, which is not the case with quartz. Quartz dust provokes a fibrogenic reaction, with only minor differences between species, in every organ capable of retaining particles and in every kind of animal which has been investigated (136, 137).

Miller & Sayers (103) found no fibrosis in guinea pigs injected intraperitoneally with asbestos and talc. Gardner (136) obtained only a very slight effect in the lungs of mice and dogs with asbestos while man, guinea pig, cat, and rat developed fibrosis. He inoculated the dog by intratracheal injection of a suspension of long chrysotile fibres in saline which failed to produce more

than minute granulomata in peripheral lymphoid tissue, although observation was continued for two years. Inhalation was employed for the mouse; asbestos bodies were formed, but the tissue response remained limited to phagocytosis over a period of two years.

Yet the dog can experience asbestosis, for Schuster (138) describes one which had inhaled dust for 10 years in a factory where three kinds of asbestos were handled. The lungs contained fibres from 8 to 60 μ long, and there was considerable diffuse, interstitial, peribronchiolar, and perivascular fibrosis. Asbestos bodies were absent.

These variations in the response to asbestos fibres are peculiar, and it is doubtful if they are genuinely a result of differences of susceptibility. For fibrous growth to be initiated, contact must be established between the stimulating agent and an area of connective tissue. It is conceivable that this contact is mechanically uncertain in the case of long fibres, especially when they are administered by the injection of a liquid suspension; more uncertain than is the case with granules of quartz.

The relationship of the immediate inflammatory reaction, which is often produced by the injection of foreign material into tissue, to the long term fibrosis also requires consideration. Kettle (139) describes a tissue response to subcutaneous injections of colloidal silicic acid which included necrosis and the ultimate development of a fibrous scar. He also produced similar lesions from the solution of silicic acid which leached out of a permeable collodion bag of silica embedded in tissue.

It is doubtful if these lesions can be regarded as analogous to the proliferating silicotic nodule. Gardner, Miller & Sayers, and other more recent experimenters, disregard any initial reaction and concentrate on the growing nodule, which is evident only after a period of weeks. Kettle's asbestos lesions referred to above (25) may come into the same category as his silicic acid scars.

Complete disregard of the variable initial reaction seems unjustified, at least in the case of asbestos, because it is doubtful if asbestosis in humans is progressive. There may be a similarity between the asbestos scar in the connective tissue under the skin, and the lung condition of asbestosis.

Physical and Chemical Factors in Pneumoconiosis

The difference between silicosis and asbestosis arises from the physical difference between the two dusts which cause them. Silicotic nodules are focal collections of large numbers of particles which have been gathered together from the distributed sites of their original deposition upon the walls of the air spaces in the lungs. The focalisation is a result of phagocyte activity and lymph currents, and it is necessary to postulate that the silica particles cannot harm the phagocytes appreciably if this description is accepted.

It is physically impossible for a long fibre, over about 20 μ, to be engulfed by a single phagocyte; hence the building up of focal aggregations of such

particles cannot take place, and the fibrosis which they produce must be diffuse.

Normally, particles over 5 or 10 μ in size are not admitted to the fine bronchioles and alveoli, since they impinge or settle under gravity upon the ciliated walls of the bronchi and bronchioles and are excreted. Fine fibres have a much greater ratio of surface area to weight than compact granules. Hence the viscous drag of the air upon their surface, which is set up when they move relative to the air, is abnormally large. They possess, therefore, a strong tendency to travel with an air stream, which explains the occurrence in lung tissue of asbestos fibres up to 250 μ long.

Asbestosis has been described as a disease of the primary lobule with silicosis as a disease of the lymph node. It is correct to go beyond this generalisation and say that both are diseases of connective tissue. The fibrosing agent must establish contact with tissue capable of producing collagen fibres. In the case of asbestosis, this is the lymphoid tissue of the primary lobule, the distribution of which has been described by Miller (140); in the case of the asbestos corn it is the connective tissue beneath the skin. In experimental pneumoconiosis it is the connective tissue of the organ inoculated with fibrogenic particles.

The inhalation of asbestos dust results in the accumulation in lymph nodes of all particles small enough to have been phagocytosed. Mild fibrous reaction has been observed from these. The long fibres are caught in the primary lobules and produce local fibrosis. The case of talc fibrosis reported by McLaughlin *et al.* (101) seems to be intermediate between the complete focalisation found with quartz dust and the complete diffuseness of asbestosis, attributable to fibres exceeding 20 μ in length. Small, scattered nodules, poorly defined, were seen which contained talc fibres up to 10 μ long but which were mainly between 4 and 5 μ. This length is probably the greatest which can be transported, and the small size, poor definition, and large number of nodules may reflect the growing difficulty of transport as the fibre length increases above 5 μ.

The electron microscope has revealed that connective tissue contains a sub-microscopic network of collagen fibrils along with intercellular material and fluid and fibre-forming cells (141). The mechanism by which the cells make fibres is not yet clear, but cytoplasmic fibres and granules (142), containing an acidic polysaccharide-protein complex, are involved and may precipitate the fibres extracellularly by a process controlled by van der Waals and electrostatic interactions with neighbouring molecules (143).

Fibres of collagen carry periodic markings having a separation of about 640 A and are similar, irrespective of their biological origin, a fact which correlates with the unspecific nature of experimental silicosis and suggests a growth mechanism common to all species.

It is still obscure how the presence of silica particles in connective tissue can stimulate the fibrogenic cells to produce collagen at an abnormal rate. The resulting nodules are similar to those of tuberculosis (144), and there

must be some feature in the chain of causation common to the crystal of quartz and the tubercle bacillus. The association of tuberculosis with dusty occupations was observed before the identification of silicosis, and the experimental increase of the local reaction to tubercle bacilli in the presence of colloidal solution of silica, itself toxic (145), is well established (146, 147).

Gye & Purdy (145) showed that the tissue change induced by silica sol administered parenterally consisted of a slow thickening of capillary boundaries by a deposit of collagen, and their work encouraged the theory that solution of silicic acid from quartz particles in the lymph tissue initiated fibrous growth. It could equally well be argued that silica would be precipitated from the colloidal solution owing to its particles aggregating at the low pH of blood and, depositing in the connective tissue irrigated by the capillaries, would initiate collagenous growth near their walls.

This view persisted for 30 years in spite of certain difficulties. Banting (148) was one of the first to distinguish clearly the peculiar nature of the growing silicotic nodule as distinct from the local toxic action, necrosis, and formation of scar tissue which followed the injection of colloidal silica sol. He showed that nodules could be produced only by particulate silica; in addition he repeated Kettle's experiment of implanting a permeable bag of silica into tissue and failed to obtain nodules. Banting's conclusion was that particulate silica caused silicosis and that fibrosis might be initiated by the phagocyte changing from an amoeboid to a connective tissue cell.

The solubility theory persisted, nevertheless, with support from the observed decrease in silica solubility caused by the presence of small amounts of iron (25) or aluminium and of larger quantities of calcium hydroxide or cement (126, 127), or by the presence of other rock dusts (128).

There was some evidence of a parallel diminution of fibrogenic action, though exceptions were noted. Reports of siliceous dusts which were failing to produce silicosis were accounted for by the assumption of a depression, by another constituent, of silica solubility, as mentioned previously, and were accepted as evidence in favour of the solubility theory.

It was also found that the fibrogenic effects of certain silicates ran parallel with their solubilities (154); the weakness in this argument lies in the indirect and unspecific association between the dust administered and the resulting fibrous growth, except in the case of free silica.

The grounds for believing that silicic acid, dissolved from particles of silica and silicate by the lung fluids, is the agent which stimulates abnormal collagen production in connective tissue are extremely tenuous. There is no positive evidence apart from the experiments of Kettle (25, 139) by subcutaneous injection of colloidal silicic acid, which must be regarded as doubtful because of the nature of his lesions; these were not growing nodules but contained areas of scar tissue repairing regions of necrosis produced by the toxic action of colloidal silicic acid; crystalline silica had a much smaller effect. Necrosis in the silicotic nodule does not precede fibrosis but is subsequent to it.

An apparent abundance of negative evidence is notably diminished when examined critically. On the one hand are the clinical reports of simple pneumoconiosis with absence of nodulation, diffuse x-ray shadowing or reticulation without discrete opacities, and long histories of exposure to siliceous dusts. These are cited as instances of the inhibition of solubility. It is imperative that accurate measurements of dust exposure and analyses of the dust should be available before a pronouncement be made in such cases. These data are invariably lacking, and it is suggested that most of the cases mentioned in this review can be accounted for in terms either of inert dust loading of the lungs or of diluted silica, with or without tuberculosis in each group.

On the other hand is the experimental work with animals. Evidence of the preventive action of a film of iron oxide upon silica particles seems to rest upon a single experiment by Kettle (25), using the method of subcutaneous injection. The effect of aluminium oxide films on solubility is definite, but King found that many low solubility dusts were pathogenic; he suggested that this might be a result of the film being dissolved away after the dust particles had deposited in the lungs (128).

The work of Gardner on carborundum dust (150) is usually quoted as supporting the solubility theory against the old idea of mechanical trauma by hard, sharp particles, a conclusion the author himself maintained; his paper describing the effects of inhaled dust of silicon carbide upon guinea pigs is worth quoting from. He is discussing the lungs of the control animals, which had inhaled dust, in comparison with others which had also inhaled tubercle bacilli of low virulence; the main mass of dust was scattered about the air spaces, and there was no fibrosis of the lung parenchyma:

> The tracheobronchial lymph nodes in both the dust controls and the injected series showed microscopic dust deposits at a somewhat later date than did the corresponding granite series; at two months an occasional particle was found, but it was not until the fourth month that any considerable quantity of dust had collected. From then on, until the sixteenth month, there was a steady increase in the deposits in both series. In the last five animals killed very large quantities were contained in all parts of the nodes. In the two dust controls of this period there was a very definite and somewhat extensive fibrosis which had obliterated the medullary sinuses. This reaction may be explained as the result of concentration of excessive amounts of irritant within a small focus.

Gardner also comments on the alteration of the course of the tuberculous process induced by the inhalation of a low virulent organism, from a self-limited process, usually healing by resolution, to a progressive tubercular bronchopneumonia.

Both the encouragement of tuberculosis and the initiation of fibrous growth in the lymph nodes, which are commonly accepted as specific attributes of silica (at least in experimental pneumonconiosis), are here described as the result of the presence of an inert dust.

The difficulty of carrying out inhalation experiments led to the use of intravenous and intratracheal injection. Gardner & Cummings (151), using the former technique, showed the importance of particle size. Particles of quartz between 6 and 12μ in size failed to produce silicotic nodules, while particles between 1 and 3μ did. The particles were transported by the blood stream to lungs, liver, and spleen; no reaction was observed in the kidneys. Necrosis and scar formation resembling that described by Kettle was produced at the site of injection in the ear.

The idea that a dust with a high specific surface was especially dangerous on account of its enhanced solubility was thus encouraged, but later experiments showed the existence of an optimum particle size for fibrosis in the region of 1 to 2μ (152, 153).

The great objection to the solubility theory of silicosis came with the discovery that the solubilities of various forms of silica did not always run parallel with their pathological effects (149, 154, 155). In the first place, it was established that samples of quartz from which an initial quantity of silicic acid could be leached readily did not thereby lose their fibrogenic effect, even though their subsequent solubility was very low. Secondly, four forms of silica, i.e., vitreous silica, quartz, cristobolite, and tridymite, have similar solubilities but produce differing fibrogenic effects, the intensities broadly increasing in the order named (156, 157).

The experiments of Kettle were conducted with colloidal solutions of silicic acid, and it is only recently that the physical chemistry of solutions of silica has been worked out sufficiently for their significance in the solubility theory of silicosis to be appreciated. Solutions of silicic acid may contain both monomeric and dimeric molecules and polymerised aggregates of sizes ranging up to the colloidal particles present in Kettle's solutions.

Molecularly dispersed solutions are excreted to a large extent after oral or intravenous administration without damage to the animal (158), and after oral administration of silica and silicates in man (159). Colloidal solutions, however, are toxic (158), precipitate protein (160), and produce scar type fibrosis, though not in the lung, from which they are too rapidly drained away (160). Policard & Collet (161) claim that the fibrosis is qualitatively similar to that produced by crystalline quartz, but quantitatively more prolific. There has thus been a tendency to accept the innocuous nature of molecular silicic acid and to associate the growth of silicotic nodules with colloidal solution.

The immediate objection to this view is that nothing remotely resembling a nodule has ever been produced by the administration of colloidal silica to animals, while human beings exposed to the dust of amorphous (not vitreous, which acts like crystalline) silica rarely develop disease unless the concentrations are abnormally high; in this case the clinical picture is quite different from silicosis (81 to 84).

These points are countered by arguing that inhaled dust of amorphous (i.e., dry, colloidal) silica is so soluble that its action in lung tissue is pro-

foundly modified, whereas classical silicosis could be attributable to the production of colloidal silicic acid *in situ* from particles of silica.

Doubt is thrown upon the last hypothesis by the failure to find amorphous silica in lung residues and by the fact that it is impossible to demonstrate the presence of colloidal silicic acid in extracts from crystalline or vitreous silica prepared under conditions which could hold in the lungs.

At high pressures and temperatures colloidal solutions are formed directly, but the quantity of silica dissolved has fallen to .02 per cent when the temperature is down to 200°C. (162). At body temperature solutions containing less than .016 per cent SiO_2 do not form a colloid; the transition from a true solution to a gel is slow in the vicinity of the above concentrations, and it is extremely unlikely that so high a figure is ever attained in tissue fluids (163).

Baumann (164) emphasised the complicated nature of solution equilibrium between crystal, colloid, and molecular phase, and the time taken to become stable; as a result, many determinations of alleged solubility were in reality measurements of rate of solution.

His figure for the solubility limit of molecular silicic acid was .012 to .014 per cent over the pH range 4.5 to 9.0, with a much higher value in more alkaline media. This figure was obtained for equilibrium between amorphous silica and solution, and it is interesting to note its closeness to the figures above for crystals at 200°C. (162) and gelling solutions prepared from sodium silicate (163).

Paterson & Wheatley (165) found the equilibrium concentration of molecular silicic acid to be .014 per cent irrespective of the presence of colloidal silica solution, but could not obtain any colloid in solutions made with crystalline silica.

A suggestive feature of these investigations is the recurrence of a figure around .014 per cent for equilibrium with both crystalline and colloidal material. It is certainly possible that the crystal surface is contaminated locally or generally with colloidal particles which are attached too strongly to float away into the solution yet provide a reservoir for maintaining the molecular equilibrium concentration.

As far as silicosis is concerned, the conclusion must be that any colloidal silica would have to be associated with the crystalline particles so closely as to necessitate their virtual contact with the fibre-forming cell in order to stimulate it. The actual amount of colloid could be extremely small.

Summary

Pneumoconiosis is the term used for a group of lung diseases caused by the accumulation of dust in the lungs without systemic effects immediately attributable to the dust. Some dusts are inert and produce neither an obvious reaction in the organ nor symptoms for diagnosis until a considerable quantity of dust has been collected. Free silica, usually in the form of quartz,

causes silicosis in which a continuous formation of collagen is stimulated in focal nodules which contain dust.

There are many reports of dusts containing quartz which have not caused silicosis; this is commonly put down to the inhibition of the fibrogenic action of quartz by other constituents of the dust which are known to decrease the solubility of quartz. Such reports, however, cannot be regarded as conclusive because there is seldom proof either of the inhalation by the victim of a sufficient concentration of quartz in particles fine enough to reach the lung alveoli, or of the presence of enough quartz in the lungs to cause the classical symptoms of silicosis. There is also a lack of parallelism in experimental silicosis between fibrogenic effect and solubility. On the other hand, there is some indication that the action of quartz in the lung is modified by the presence of a sufficient quantity of an inert diluent.

The production of developing fibrous growth in the lungs by inhaled dusts of crystalline or amorphous silicates is extremely doubtful. As naturally occurring, these dusts often contain free silica, and the presence of tuberculous infection may simulate silicosis. Fibrosis produced experimentally by these dusts is usually less than that produced by quartz and less focal. The experimental techniques are drastic and might be expected to produce such a reaction more readily than would be the case with long continued inhalation. Even inert dusts are suspected of encouraging the development of tuberculosis.

There are thus grounds for thinking that quartz and other forms of crystalline or vitreous silica are unique in causing proliferating fibrous nodules in connective tissue. The only other dusts which cause rapidly developing collagenous growth are fibrous silicates, loosely termed asbestos. The pathology of asbestosis contrasts with silicosis because the physical nature of the fibres renders them liable to become caught in the fine airways of the primary lobule. It is possible that chemical factors are concerned in the ensuing fibrosis which seems to lack the active progression of silicosis. Colloidal silicic acid is a tissue poison and has been suspected as the cause of silicosis, but the effects it produces lack characteristic features of the disease attributable to quartz dust, and it is doubtful if it can be formed by the solution of quartz in the lungs.

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HEMODYNAMIC EFFECTS OF ETHER, CYCLOPROPANE, OR BARBITURATES[1]

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ETHER

Central Effects

Myocardium.—"It has been found in studying the effect of ether anesthesia on the cardiac output that all of the increase could not be due to the effect of changes in the reaction of the blood and that there is a direct stimulating action by either on the heart was assumed" (6). This quotation is consistent with widely held opinion, even up to the present day. The mass of experimental evidence now accumulated dose not support it (4, 7, 10, 20, 22, 49).

Cattell (10) in 1923 reported observations on cats and the isolated heart of cold-blooded animals showing that ether from the very beginning of its administration results in depression of the heart and decrease in its output. Gordh (22), working with rabbits and with human beings, concluded that there is a direct weakening action of ether on the heart muscle. Using a modified Starling heart-lung preparation in dogs, Fisher and co-workers (4, 20) measured aortic pressure, cardiac output, right atrial pressure and ventricular volume. The concentration of ether in the perfusing blood was determined to maintain levels consistent with light-to-very-deep anesthesia. They found ventricular dilatation at all anesthetic ranges of ether concentration and noted that the changes in dynamics produced were those of a failing heart. Again, using the Starling heart-lung preparation in dogs, Prime & Gray (49) observed a consistent depression of myocardial activity. This is an excellent paper and is highly pertinent to the topic of this review. Boniface, Brown & Kronen (7) recently reported the results of ingenious experiments involving the application of a strain gage to the myocardium in dogs. After a period of recovery it was possible for the authors to make direct observations of the contractile force of the heart under various experimental conditions. With deepening ether anesthesia there was a progressive decrease in the force, though a slight increase during induction was noted. They are of the opinion that the increase in cardiac force probably was a result of sympathetic activity.

Cardiac output.—The effect of ether anesthesia on cardiac output in dogs was found by Blalock (5) in 1927 to be an increase in all but three of thirteen dogs. These three were deeply anesthetized at the time of the determinations

[1] The survey of the literature pertaining to this review was completed in July, 1956.

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which were made by the direct Fick method. Johnson (34) in 1951 concluded that cardiac output probably is unaffected by light ether anesthesia, but rises in brief, deep anesthesia and falls during prolonged anesthesia. The stroke volume is moderately reduced. Prime & Gray (49), after observations on human beings in which the Fick principle for determinations of cardiac output was applied, found a variable rise in cardiac output during ether anesthesia, with a subsequent progressive decline during prolonged anesthesia. Brewster & Isaacs (9) in 1953 published an excellent paper reporting cardiac output estimated by the direct Fick method in intact dogs, "acutely adrenalectomized" dogs, and "acutely adrenalectomized" dogs in which total epidural sympathetic block was maintained. Cardiac output increased as much as 241 per cent when the concentration of ether in arterial blood was 91 to 100 mg. per 100 cc. in the normal dogs. After adrenalectomy the peak increase was only 19 per cent at values of 51 to 70 mg. of ether per 100 cc. of blood. The increase fell to control values at values of 71 to 90 mg. of ether per 100 cc., and declined progressively below control values in the adrenalectomized dogs with total sympathetic block. The authors conclude that when the release of epinephrine and nor-epinephrine is reduced or abolished, the effect of ether anesthesia upon the heart is myocardial depression. In a thesis published in 1955, Fletcher (21) reported his observations of 11 persons undergoing surgery. He found that the cardiac index during early ether anesthesia is decreased 26 per cent if induction is "smooth" and increased 42 per cent if induction is "stormy." During late anesthesia there was a decrease of 28 per cent with smooth induction, and an increase of 26 per cent after stormy induction.

Vascular Effects

Many studies have been made of the effect of ether on the peripheral vascular bed. As early as 1909 Derouaux (13) concluded that the fall in pressure seen after the injection of ether intravenously is attributable to vasodilation as well as to the depressive action of ether on the heart. This is at odds with the opinion of Cattell in 1923, who reasoned that ether brings about a contraction of the peripheral vessels caused by either a direct stimulation of the vasomotor center or a reflex from the fall in pressure resulting from a depression of the heart, or both. Zweifach, Hershey and other collaborators have published papers, beginning in 1945 (32, 33, 59), reporting the results of observations of the vascular bed of the omentum in dogs undergoing anesthesia. They conclude that ether anesthesia causes a marked deviation from the normal responses of the omental vascular bed. Blood flow becomes very poor, vasomotion is depressed, and epinephrine reactivity shows a gradual decrement. Johnson (34) reports a decrease in peripheral resistance during ether anesthesia in human beings and concludes that the fall in blood pressure observed probably is attributable to vasodilation. Van den Brenk and his associates (55), working with a Sandison-Clark window in the ear of rabbits and observing under direct microscopic vision the

behavior of blood vessels with intact innervation, report that arterial constriction takes place with very light ether anesthesia, while arterial dilatation occurs as depth of anesthesia increases.

Blood Pressure Effects

Many authors have reported observations of arterial blood pressure during ether anesthesia and are in general agreement that the blood pressure declines as the depth of ether anesthesia increases (10, 22, 28, 34, 50). In a very interesting recent report, Robertson, Swan & Whitteridge (52) offer data obtained from single-fiber preparations of the carotid-sinus nerve in cats subjected to anesthesia. They conclude that ether increases the sensitivity of the carotid sinus and aortic baroreceptors. This constitutes further evidence in support of the now generally accepted contention that the decreases in blood pressure observed during ether anesthesia are the results of direct myocardial depression and peripheral vasomotor inhibition. Gordh (22), measuring venous pressure from the cubital vein, reported no change except when heart failure occurred. Johnson (34), in observations on human beings, states that the pulmonary artery pressure rises considerably with ether anesthesia and is unaffected by duration or depth. He attributes the rise to pulmonary arterial vasoconstriction. Fisher *et al.* (20), using the Starling heart-lung preparation in dogs, observed an increase in auricular and pulmonary pressure when ether concentrations consistent with second-plane anesthesia were found in the perfusing blood. Brewster & Isaacs (9) report an increase in the right and left auricular pressure with decreases in cardiac output in their dogs subjected to ether anesthesia. They offer these observations in support of their contention that ether causes direct myocardial depression. Fletcher (21) in his study of human beings undergoing surgery found generally significant changes in central venous pressure, changes ranging from -5 to $+16$ mm. Hg from preanesthetic observations.

Miscellaneous Effects

Two papers were reviewed in which data were presented concerning the "central blood volume" or "pulmonary blood volume" in human beings undergoing ether anesthesia (21, 34). Johnson (34) found the pulmonary blood volume diminished during deep or prolonged ether anesthesia. Fletcher in his thesis (21) estimated the "central blood volume" to be increased by 23 per cent early in anesthesia, and to decrease gradually to control levels later.

Studies of plasma volume in man were made by Price, Helrich & Conner (47), using T-1824, radioactive chromium-tagged red cells and hematocrit determinations to assess volume changes in the various blood fractions. In general, they found that significant increases in arterial and venous pressures could be related to decreases in plasma volume during ether anesthesia. The authors postulated that there is a parallel increase in intracapillary pressure, with loss of fluid to the extracellular space as a result of increasing venous

pressure during ether anesthesia. In man this accounts for variations in plasma volume.

CYCLOPROPANE

Central Effects

Myocardium.—The common belief that cyclopropane depresses the myocardium is strongly supported by experimental observations on the heart-lung preparation in cats, dogs, and human beings under the influence of this anesthetic agent. Brace, Scherf & Spire (8) have demonstrated a marked dilatation of the heart by means of cardiac plethysmography after the administration of cyclopropane to dogs in concentrations of 50 to 75 per cent with oxygen. Moe *et al.* (40) estimated the degree of myocardial sufficiency by relating venous pressure to aortic pressure in dogs subjected to cyclopropane anesthesia. Diminished cardiac reserve occurred at concentrations of cyclopropane of less than 15 per cent, and the diminution was severe at concentrations of 25 to 35 per cent. Fisher, Bennett & Allahwala (20), in their study of the influence of inhaled anesthetic agents on the isolated heart-lung preparation, used ventricular volume as a measure of myocardial depression. They noted that cyclopropane in anesthetic ranges causes a definite dilatation of the heart, but not so much as that produced by ether. Boniface and his co-workers (7) measured heart contractile force by insertion of a strain-gage arch into the ventricle. There was a progressive increase in contractile force as anesthesia was deepened. The mechanical ability of the heart was calculated by Price & Helrich (46) as the slope of the line relating cardiac output to right atrial pressure in the dog heart-lung preparation. Arterial pressure was maintained constant. The concentration of the cyclopropane and the pH of the blood were determined. They estimated that the myocardium was depressed by 54 per cent with concentrations of cyclopropane in the perfusing blood of 15 mg. per 100 cc. Cyclopropane in clinical doses invariably depresses myocardial activity in the dog heart-lung preparation, according to Prime & Gray (49).

Cardiac output.—Greisheimer and her colleagues (25, 26, 27) determined cardiac output in dogs under cyclopropane anesthesia by the dye-dilution method. There was a slight increase in this value as depth of anesthesia increased. When thiopental sodium was used as an induction agent, cardiac output increased, only to decrease after cyclopropane was added as the maintenance agent. Addition of ether to the mixture of cyclopropane anesthetizing dogs had the effect of increasing cardiac output. No preanesthesia control studies were reported. Robbins & Baxter (51) determined cardiac output in nine intact dogs by application of the Fick principle. Cardiac output increased in all dogs during moderately deep surgical anesthesia but decreased to normal or lower values during very deep anesthesia. Concentrations of cyclopropane in the blood ranged from 20 to nearly 30 mg. per 100 cc. Prime & Gray (49) observed that the initial effect of cyclopropane is to increase the cardiac output, but over a period a gradual decline

was noted in human beings. Lee and co-workers (37) observed a decrease in cardiac output in six human beings soon after the induction of light cyclopropane anesthesia. During the next two hours cardiac output continued to decrease slightly. They used the Hamilton dye-dilution method. Etsten and co-workers (18) administered cyclopropane to 13 human beings, producing light surgical levels as evidenced by the electroencephalogram and concentrations of cyclopropane in the blood of approximately 10 mg. per 100 cc. Cardiac index measured by the dye-dilution method decreased a mean of 22 per cent. In a later paper (17) Etsten *et al.* said they found no significant decrease in cardiac index during anesthesia with cyclopropane to electroencephalographic level III in human beings breathing spontaneously. Thompson *et al.* (54) observed the cardiac index in seven surgical patients in the conscious state and during induction of anesthesia to light and deep levels, and in emergence to light levels. A decrease in cardiac index was consistently seen with induction of light anesthesia, and a further decrease was noted in most patients as deep anesthesia was reached. With emergence to light levels, there was a rapid return of values for cardiac index toward the initial observation. Level of anesthesia was ascertained by means of the electroencephalogram, and the cardiac index was determined by the dye-dilution method.

Vascular Effects

Observations were reported by Hershey and co-workers (32, 33,59),who studied the capillary bed in the omentum of the dog. During light and moderately deep anesthesia with cyclopropane there was little or no interference with vascular activity. During deep anesthesia there was marked interference with peripheral vascular activity. The degree of interference with cyclopropane during all levels of anesthesia was less than that with ether and with thiopental sodium, which were also investigated. Direct observation of the vessels in the ear of the rabbit with a Sandison-Clark chamber, by van den Brenk and his associates (55), demonstrated that with the administration of 50 per cent cyclopropane and oxygen, arterial constriction was observed and that this persisted for more than 10 min. after the rabbit began to breathe air again.

Observations on peripheral blood flow include those of Prime & Gray (49) and those of Lee and his associates (37), both of whom found a marked increase in the flow of blood in the forearm in human beings shortly after the induction of anesthesia with cyclopropane. With maintenance of anesthesia there was a gradual decline in the blood flow toward initial observations. A similar increase in blood flow has been observed by Abramson *et al.* (1) in the hand and forearm during anesthesia with cyclopropane. Bennett *et al.* (3) have reported observations, during anesthesia with cyclopropane, of the flow of blood in femoral and carotid arteries and in the superior mesenteric veins of dogs. They observed a reduction in femoral blood flow, while flow in the carotid and mesenteric areas increased. Other evidence in favor

of variation in peripheral vascular activity during anesthesia with cyclopropane has been offered in reports by several authors of variations in total peripheral resistance. Greisheimer and her colleagues (25, 26, 27) reported little change in total peripheral resistance during anesthesia with cyclopropane and oxygen in dogs. Etsten *et al.* (18), in a group of 13 human beings, noted that total peripheral resistance increased a mean of 56 per cent during light surgical anesthesia with cyclopropane. However, in a later study (17) he and his associates found no significant increase in the total peripheral resistance in patients lightly anesthetized with cyclopropane when they were breathing spontaneously. Thompson *et al.* (54), on the other hand, in their studies found a marked increase in peripheral resistance with the onset of light anesthesia and a further increase as deep anesthesia was induced.

Effects on Blood Pressure

Considerable variation is evident in the reports on changes in blood pressure during anesthesia with cyclopropane both in human beings and in animals. This may result from inability on the part of many investigators to control the administration of anesthesia. This is exemplified in a paper by Price and his colleagues (48) in which they demonstrated no consistent effect of cyclopropane on arterial blood pressure in 12 human beings breathing spontaneously. However, with imposition of positive pressure in the airway, there was a decrease in arterial blood pressure during light anesthesia with cyclopropane, although no change or a very slight increase was observed during anesthesia with ether. Etsten *et al.* (17), on the other hand, observed an increase in mean blood pressure during spontaneous respiration with cyclopropane. This was associated with a significant increase in carbon-dioxide tension. During controlled respiration mean blood pressure was the same as the value obtained during the conscious state, and CO_2 returned to normal.

There appears to be agreement among most investigators that during anesthesia with cyclopropane there is an increase in central venous pressure. Price, Conner & Dripps (44) attempted to relate this increase to respiratory variations and the state of acid-base balance. They found that venous pressure was elevated with normal and with increased carbon dioxide tension, but that the increase in venous pressure was greater when carbon dioxide tension was increased above normal. They were able to correlate the increase in central venous pressure directly with increased concentrations of cyclopropane in the blood.

Miscellaneous Effects

Price, Helrich & Conner, in a later paper (47), proposed that the increase in venous pressure observed with deep cyclopropane anesthesia was responsible for a significantly reduced plasma volume in patients to whom cyclopropane had been administered.

BARBITURATES

Central Effects

Myocardium.—There is almost complete unanimity of opinion among those who have investigated the subject that the barbiturates administered intravenously in doses sufficient to produce anesthesia act as direct cardiac depressants (12, 15, 22, 34, 46, 49). Das (12) in 1941 found depression of the auricle strip of frogs with dilutions of hexobarbital (Evipan) as great as 1 in 50,000. He presented myocardiographic evidence that the heart of the cat *in situ* is similarly affected, even with small doses of the same drug. Gordh (22), in an extensive report in 1945 based on work with rabbits and human beings, was of the opinion that during deep anesthesia the reserve power of the heart is diminished. Johnson (34) in 1951, after studies on six patients anesthetized with a brominated, methylated barbiturate (Narkotal), found that the power of both the right and left ventricle was depressed. Prime & Gray (49) in 1952, working both with the Starling heart-lung preparation in dogs and with human beings, reported that clinical doses of thiopental sodium invariably depress myocardial activity. Price & Helrich (46) in 1955 estimated the mechanical ability of the heart of the dog in a heart-lung preparation as the slope of a line relating cardiac output to right atrial pressure. By these criteria they found that thiopental sodium in a concentration of 2.2 mg. per 100 cc. depresses myocardial activity 32 per cent. It is of interest that this was significantly lower than the percentage depression reported for ether, cyclopropane, nitrous oxide and acidosis. As a result of their studies on 15 patients reported in 1955, Elder and his co-workers (15) postulated that myocardial depression takes place under anesthesia with thiopental sodium.

Cardiac output.—Among the authors reviewed, only Greisheimer and her co-workers (23, 24) reported an increase in cardiac output under anesthesia with thiopental sodium. Their observations were made upon dogs. In studying the effect of Narkotal on six patients, Johnson (34) found that the stroke volume was reduced. His methods were the Fick and the Hamilton dye-dilution technics. Prime & Gray (49) determined cardiac output in human beings on the basis of the Fick principle, findings that, unlike cyclopropane and ether, thiopental sodium produces a reduction in cardiac index. Li *et al.* (38, 39), studying 15 subjects under anesthesia with thiopental sodium, determined that at surgical levels of anesthesia determined by electroencephalogram there was a 25 per cent reduction in the cardiac index. Price & Helrich (46), with dog heart-lung preparations, found a reduction in cardiac output took place when the preparation was perfused with blood containing thiopental sodium in the concentration of approximately 2.2 mg. per 100 cc. Elder and his co-authors (15) reported a consistent decrease in cardiac output in a study of 15 patients undergoing anesthesia with thiopental sodium, nitrous oxide and oxygen. In 1954 Page and co-workers (42) reported studies of cardiac output by the dye-dilution method in dogs undergoing pentobarbital anesthesia and found no significant change. Etsten, Li

& Fisher (16, 38), after studies on dogs and human beings with the use of both the dye-dilution and Fick methods, are of the opinion that cardiac output is progressively depressed as the depth of anesthesia with thiopental sodium increases. These findings in respect to human beings were consistent with those of Fieldman (19), who in 1955 reported observations on 13 patients undergoing surgery with thiopental anesthesia and anesthesia depth control with electroencephalogram. Pollock *et al.* (43) in 1955 made a study of cardiac output as calculated from ballistocardiograms of 20 women. They found no change under anesthesia with thiopental sodium, nitrous oxide and oxygen.

Vascular Effects

Das (12), in cat-leg perfusion studies, found evidence of vasodilation and vasomotor depression. Beecher *et al.* (2, 3), in a report of the effect of hexobarbital on dogs in 1944, reported increased femoral, carotid and mesenteric blood flow. Zweifach, Hershey and co-authors (32, 33, 59) determined initially the appearance of vasoexcitor material in the blood of dogs undergoing anesthesia with thiopental sodium, and later the appearance of vasodepressor material. All phases of vasomotion were depressed by anesthesia with thiopental sodium. The preparations used in this study were the omentums of dogs under direct microscopic observation. Gordh (22), in his study of rabbits and human beings, postulated the occurrence of peripheral vasomotor paralysis as a result of barbiturate anesthesia. Price *et al.* (45), after a study of the response to increased airway pressure among six patients, suggested that there may be inadequate vasomotor response to hypotension under anesthesia with thiopental sodium. In this regard their findings were in contrast to those made with cyclopropane. Prime & Gray (49) found the flow of blood in the forearm to be increased under anesthesia with thiopental sodium, nitrous oxide and oxygen, and curare. Greisheimer and co-workers (23), in an attempt to relate the concentration of thiopental sodium to hemodynamic effects, found decreased peripheral resistance with accompanying increased cardiac output in their experimental dogs. Kory & Mabe (36), investigating the effect of sodium amytal on 14 hypertensive males, concluded that there was a decrease in the total peripheral resistance as light sleep was induced. Van den Brenk and his co-authors (55), using a Sandison-Clark window in the ear of a rabbit to make possible direct observation of innervated peripheral vessels, demonstrated arterial dilatation and diminished vascular tone at a dose of thiopental sodium of 20 mg. per kg. of body weight. The reviewers have found only one paper in which the authors reported an increase in peripheral resistance in hemodynamic studies of dogs undergoing barbiturate anesthesia. In this case, however, the agent used was pentobarbital sodium, 30 mg. per kg. of body weight. Fieldman (19), in his study of patients undergoing anesthesia with thiopental sodium, reported an increase in peripheral resistance only after deep anesthesia as estimated by electroencephalogram. Further, he postulated that peripheral pooling of the blood takes place when

this drug is used. In two articles Kety and co-workers (35, 57) found no significant change in cerebral blood flow under "semi-narcosis" with thiopental sodium, but noted that there is a slight increase under light anesthesia with this agent (54 ml. per 100 gm. per min. to 61 ml. per 100 gm. per min.). They found the cerebral vascular resistance slightly reduced and postulated that these changes may be a result of increased carbon dioxide tension in the arterial blood.

Miscellaneous Effects

Some studies have been made which include calculations of "central blood volume" or "pulmonary blood volume" (19, 34, 38, 42). All studies done with thiopental sodium in human beings reveal a reduction in this value. The only finding of an unchanged central blood volume was in a study on dogs in which the barbiturate used was pentobarbital sodium, 30 mg. per kg. of body weight [Page *et al.* (42)].

Price, Helrich & Conner (47), in a study in human beings, related plasma volume to venous and arterial pressures in patients undergoing anesthesia with cyclopropane, ether and thiopental sodium. They found decreases in venous and arterial pressure when thiopental sodium was used, related to increases in plasma volume. This was not so in the case of the other two agents.

DISCUSSION

In any attempt to evaluate the importance and validity of the work reported in this review, it is important that the reader have some understanding of the validity of certain of the methods used and possible interpretations of some of the parameters defined. Many excellent background articles of this kind appear in the literature. (11, 14, 27 to 31, 38, 41, 43, 53, 56, 58).

On the basis of the articles reviewed, and considering only the three anesthetic agents to which this paper is devoted, it seems fair to conclude that all three produce some degree of myocardial depression. Thiopental sodium appears to induce the most marked interference with the peripheral vascular system, leading to generalized pooling of peripheral blood. This effect is least noticed during anesthesia with cyclopropane. The application of conclusions drawn from the results of experimentation on animals to human beings undergoing anesthesia must be made with great care.

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RADIOACTIVE ISOTOPES IN MEDICINE[1,2]

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That there is widespread and growing interest in the medical uses of the radioactive isotopes is well demonstrated by the fact that this article will be the first published in the *Annual Review of Medicine* entirely devoted to their clinical applications. A recent report of the United States Atomic Energy Commission documents the very rapid increase which has occurred in the number of medical institutions licensed to use radioisotopes for research or therapy or both, and the tremendous increase in the actual amount of radioactive isotopes shipped for these purposes (1). It also contains more than 4500 references to publications in the life-science fields wherein radioactive isotopes were used, and this covers only the three and one-half year period ending in February, 1955. Medical research and clinical work in this field is by no means limited to the United States, and the tremendous volume of work being done in Europe, Asia, and South America is reflected in excellent reviews by Mayneord, Koslova, Mitchell, and many others (170 to 189). Since so much work is being done with the radioisotopes now, only those reports concerning the more important clinical uses of the isotopes will be covered in this review.

GENERAL CONSIDERATIONS

There are several factors which limit the use of radioactive isotopes in medical research, diagnosis, and therapy, and it may be well to review them at this time. A more complete discussion has been given by Hahn (2). The chemistry, pharmacology, and radiation spectrum of the element must be known. Toxicity of the isotope itself, or of elements formed during its production and present as contaminants, or produced as "daughter" compounds during its radioactive decay will greatly reduce its usefulness in biological systems. Specific localization in certain tissues, such as the concentration of iodine isotopes in the thyroid gland, or strontium in growing bone may be advantageous or undesirable, depending on the specific situation under consideration.

The type of radiation emitted is of the utmost importance. For therapeutic use, alpha emitters would be best, since alpha particles penetrate tissue for only minute distances and give very high specific ionization along their path. Therefore, the radiation effect would be limited virtually to the

[1] The survey of the literature pertaining to this review was completed in September, 1956.

[2] The following abbreviations are used in this review: PBI (protein-bound iodine); TSH (thyroid stimulating hormone).

cell containing the isotope. However, most isotopes which decay by alpha emission are highly toxic and have very long half-lives. Gamma emitters, because of the great penetration of their radiation, are useful only in situations where a more widespread, generalized radiation effect is desired. Their radiation, although easily counted on the surface of the intact body because of this penetrability, is not confined to any one tissue or organ. Beta particle emitters are the best compromise at present, since beta particles travel only a few millimeters in tissue, at most, and localized radiation can be achieved. Also, shielding problems are not great, and there are many beta-emitting isotopes which are not toxic per se.

The radioactive half-life of the isotope is also of great importance in determining its usefulness. Those with short half-lives are uneconomical to transport large distances from their production site. If they are used, large amounts of activity must be present initially in order to have enough left for the desired task at the final destination, and this poses problems in personnel protection and excessive shipping weight as a result of the magnitude of the required shielding. Isotopes with long half-lives are potentially carcinogenic, and if the specific activity is low, such a large amount of material might be required as to be pharmacologically toxic. The most suitable range for the half-life of an isotope which will be used in medicine is from 10 hr. to 30 days, although there are some exceptions to this statement.

Finally, the specific activity (ratio of radioactive atoms to stable atoms of the same element) obtained in the production of the isotope is a limiting factor in its use. For tracer studies, where only minute quantities of an element can be introduced without altering the content of that element in the body, isotopes of low specific activity are useless and give misleading results.

Radioiodine in the Diagnosis of Thyroid Disease

The most widely used radioisotope in the field of medicine today is radioactive iodine, I^{131}. Since the early investigations of Hamilton & Soley (3) and Hertz, Roberts & Evans (4) a truly enormous volume of literature has been published describing studies of almost every aspect of the normal physiology, functional pathology, and therapeutics of the thyroid gland, utilizing I^{131}. The proceedings of the symposium held at the Brookhaven Laboratory (5) and the recently published book edited by Werner (6) thoroughly review the present status of our knowledge concerning the thyroid gland.

Numerous tests have been suggested to differentiate between euthyroidism, hypothyroidism, and hyperthyroidism. Stanley & Astwood (7) measured the rate of thyroidal uptake of I^{131} (accumulation gradient method), whereas Werner *et al.* (8, 9) advocate the simple measurement of the percentage of the administered dose of I^{131} found in the thyroid gland after a specified time interval. Skanse measured the amount of radioiodine excreted in the urine (10), and Keating *et al.* (11) measured the urinary excretion rate to arrive at some conclusion regarding the functional state of the thyroid.

Myant, Pochin & Goldie in England (12) and Berson and co-workers in this country (13) have employed a method which measures the plasma iodide clearance rate of the thyroid, and they claim better resolution of the hyperthyroid from the euthyroid group by this means. Silver, Fieber & Yohalem (14) have measured the amount of I^{131} circulating as protein-bound iodine (PBI) 72 hr. after an oral tracer dose, while Clark *et al.* (15) have determined the PBI conversion ratio (ratio of PBI^{131} to total serum I^{131}), and they also claim good discrimination for their methods.

The fact that so many methods have been developed to measure the functional state of the thyroid should make one suspect that no single test is really satisfactory, and such indeed is the case. Although the urine excretion tests are easy and convenient, errors and inaccuracies in collecting the specimens introduce such uncertainty as to make them unreliable. The thyroidal iodide clearance rate is independent of alterations in kidney function, which can markedly affect the gross thyroid uptake tests, but it is not as simple to measure as the thyroid uptake of I^{131}.

There are many factors which influence the accuracy and reliability of these tests in addition to the usual technical errors inherent in any measurement. Stanbury *et al.* have found that long residence in an endemic goiter area may result in uptake studies characteristic of hyperthyroidism, in spite of obvious clinical and other laboratory evidence of euthyroidism (16). Previous medication with iodides (17), desiccated thyroid (18), thyroxine (19), and triiodothyronine (17) will produce a falsely low I^{131} uptake in a euthyroid individual. Propylthiouracil, by blocking organic binding of iodine in the thyroid, produces a low uptake in the gland, but since the iodine-concentrating mechanism is not affected, the accumulation rate measurement is normal (20). Silver (21) and Paley (22) have studied the various tests in patients with hyperthyroidism before and after treatment, either with surgery or radioiodine. Both found the PBI^{131} test to be unreliable after therapy, and Silver particularly emphasized the need for the physician to be a clinician as well as a scientist and laboratory worker and to rely most heavily on his clinical judgment in cases where the laboratory data are confusing or conflicting.

There have been several other reports evaluating the usefulness and reliability of the different thyroid function tests. Chapman & Maloof (23), in an excellent review of their 10 years' experience with radioiodine, report that the thyroid uptake test is more informative than the chemical PBI determination and basal metabolic rate measurement. Storaasli and others (24) studied 132 patients by means of the 2 hr. and 24 hr. thyroid uptake tests and the thyroid iodide clearance rate. They report only a slight difference between the 24 hr. uptake and the thyroid clearance rates in distinguishing euthyroid from hyperthyroid individuals. They feel that on theoretical grounds, the clearance method is more reliable, since it is less likely to be influenced by other physiological conditions. However, they also note that the test is time-consuming and that 85 per cent of the patients

could be adequately classified on the basis of the 24 hr. uptake test alone.

McConahey, Owen & Keating (25) compared seven diagnostic radioiodine tests simultaneously in a large group of patients with either no thyroid disease, nontoxic goiter, adenomatous goiter with hyperthyroidism, exophthalmic goiter, or myxedema. In their study, the most reliable tests for the diagnosis of hyperthyroidism were the 6 hr. thyroid uptake of I^{131} and the thyroidal iodide clearance. Since the uptake test was the simplest and quickest and required the least radioactivity it was thought to be the best for routine screening. They also found that only the 6 hr. and 24 hr. thyroid uptake tests were of value in establishing a diagnosis of myxedema and that none of the I^{131} tests were of real value in determining whether a patient with a nodular goiter was hyperthyroid.

Beck, Kronsbein & Hobbs (26) in a similar study also reported the superiority of the simple thyroid uptake test, measured at 4 or 8 hr. after administration of the tracer dose of I^{131}, with the counting tube 30 cm. from the neck. They found that the thyroid iodide clearance method gave poor discrimination of the euthyroid from the hyperthyroid groups.

Because this overlapping is present to some degree in all tests, more complicated procedures have been suggested to clarify the diagnosis in patients whose initial results are in an equivocal range. Greer & Smith (27) found that by giving desiccated thyroid (2 grains per day) to such people for one week, and then repeating the uptake studies, good differentiation was achieved. Euthyroids had 24 hr. uptakes of less than 20 per cent, whereas there was little change in those patients with hyperthyroidism. Papper reports similar results after giving 0.2 to 0.4 mg. of l-thyroxine (19), and Werner also had comparable data using 0.070 mg. of triiodothyronine per day (17). Werner has also reported that patients who were judged to be euthyroid by all the usual clinical and laboratory tests, yet displayed the eye signs of Graves' disease, fell into the hyperthyroid group when given I^{131} uptake tests before and after triiodothyronine (28). He feels that it is likely that such patients will eventually develop the full-blown clinical picture of exophthalmic goiter.

Use has also been made of an active preparation of the thyrotropic hormone of the anterior pituitary (TSH) to eliminate uncertainties in the diagnosis when uptake results fall into the range of 10 to 20 per cent, a zone where there is overlapping between the hypothyroid and euthyroid groups. Jeffries *et al.* (29) achieved good separation of the two groups by doing a 3 hr. thyroid uptake test, injecting 4 U.S.P. units of TSH, and then 24 hr. later, doing a second 3 hr. uptake measurement, after correcting for residual activity in the thyroid. Bishropric (30) confirmed the value of this procedure, but he felt that 24 hr. uptakes were of more value than 3 hr. tests. Euthyroid patients, or patients whose thyroids have been suppressed by thyroid medication, will have an increase of at least 10 percentage units in the second uptake test, and the second value will be 15 per cent or higher. Patients with primary hypothyroidism will have either no response or a

much smaller response to the TSH injection. Querido & Stanbury (31) and Schneeberg, Perloff & Levy (32) have used similar methods to distinguish primary myxedema from secondary (or pituitary) hypothyroidism. Usually, the patient is given from three to five daily injections of 10 units of TSH before the second uptake test is carried out. Those with primary hypothyroidism have a morphologically damaged thyroid and fail to respond to the TSH. Patients with pituitary myxedema have a gland which is histologically normal but hypofunctioning; it can and usually does respond to the exogenous TSH stimulation. Since patients with pituitary myxedema usually have some degree of adrenal insufficiency too and are very sensitive to the effects of thyroid hormone, care must be taken not to precipitate an adrenal crisis.

Skillern has recently reported on the value of the TSH test in distinguishing struma lymphomatosa from nontoxic adenomatous goiter (33). He found that in 18 patients with proved struma lymphomatosa not one had an increased thyroid uptake of I^{131} after 4 units of TSH, whereas 18 patients with nontoxic adenomatous goiters all had an increased uptake after TSH, provided their initial uptake was less than 60 per cent. The two categories were not separable on the basis of clinical examination and routine thyroid function tests but only by the TSH test.

Recently, another isotope of iodine, I^{132}, has become available for use in studying thyroid function and physiology (34, 35). This isotope has a shorter half-life than I^{131} (2.33 hours versus 8 days) and a more energetic radiation spectrum. The former far outbalances the latter in determining the radiation dosage, and a reduction of thyroid radiation by a factor of 30 to 100 is obtained when I^{132} is used instead of I^{131}, at equivalent doses. Body radiation is reduced by a factor of at least 15 (36). Thus it would be much safer to use I^{132} in doing diagnostic studies on children or in patients where repeated tests will be made. Since it has such a short half-life, it cannot be used for those tests of thyroid function requiring several days (PBI^{131} plasma conversion ratio). It is obtained from a portable generator charged with $tellurium^{132}$ and "milked" from it as needed by a simple process. Thus, laboratories quite remote from the production site may use I^{132} without excessive losses in activity as a result of time spent in transit. As yet, little work has been reported utilizing I^{132}, but it is certain to become more widely used.

Radioiodine Treatment of Hyperthyroidism

In 1942 Hamilton and Lawrence in California and Hertz and Roberts in Massachusetts reported the first human cases of thyrotoxicosis treated with radioiodine. Since then, a vast experience has been gained with this mode of therapy, and there are many excellent surveys of the methods used and the results obtained (37 to 44, 190 to 196). There is almost universal agreement that radioiodine is safe, effective, and gives results equal to, if not better than, thyroidectomy at the hands of a skilled surgeon. McCullagh, in

a concise review (44), lists the following advantages: (*a*) no mortality; (*b*) no vocal cord paralysis; (*c*) no permanent tetany; (*d*) control achieved in almost 100 per cent of the patients; (*e*) thyroid size usually reduced to normal; (*f*) no discomfort; (*g*) no time lost from work and no disability from treatment; and (*h*) recurrence is rare and can be easily treated with more I^{131}. Although some increase in symptoms may occur two to five days after treatment, only one case of true thyroid crisis with a fatal outcome has been reported (37). Tighe (45) has reported the only case of hypoparathyroidism after radioactive iodine treatment for thyrotoxicosis, and this was only temporary.

The only disadvantages are: (*a*) the possibility of inadequate therapy at the first dose, needlessly prolonging the toxic state and its accompanying dangers; (*b*) the possibility of producing posttreatment myxedema; and (*c*) the possibility of having a carcinoma develop in the thyroid many years after the radioiodine treatment.

The first two are related to the difficulty in estimating the correct dose of I^{131}. The most important factors in deciding what dose to give are: (*a*) the weight of the thyroid gland; (*b*) the uptake by the gland; (*c*) the age of the patient; and (*d*) the severity of the disease and the urgency in controlling toxicity rapidly. Estimations of thyroid weight are notoriously inaccurate (46), and large errors may be present. In addition, the distribution of activity in the gland and the effective half-life of I^{131} in the thyroid will also affect the clinical result, and neither can be accurately predicted.

The third factor, possible carcinogenic action of I^{131}, is still not definitely settled. No carcinomas have been found as yet in patients given I^{131} for hyperthyroidism. Furth & Tullis (47) discussed this problem at length and concluded that this factor should not be a deterrent to treatment with I^{131}. They did state that combined treatment with radioiodine and thiouracil-like compounds seemed highly hazardous, a conclusion based on animal work previously reported by Doniach (48) and Goldberg & Chaikoff (49). Although four cases of acute leukemia have been reported in patients treated with I^{131} for thyroid carcinoma (50, 51, 197), Seidlin's group analyzed the problem and concluded that in the doses ordinarily employed in the treatment of hyperthyroidism, no increase in the incidence of leukemia should be found (52). King *et al.* have reported a case in which a primary carcinoma of the larynx appeared in a woman who had received I^{131} therapy for a thyroid cancer (53). However, only about 12 months elapsed between the first dose of radioiodine and detection of the laryngeal tumor, and considering the usual time relationships in radiation-induced neoplasms in humans this seems much too short to incriminate the I^{131} as a causative agent.

Since the final evaluation of the carcinogenicity of radiothyroidectomy will not be made for another 10 to 20 years, many groups restrict its use in uncomplicated cases to patients over the age of 40 (42, 43), and at the Donner Clinic we tend to follow this policy too. Others feel that there is no basis for this fear, and place no age restrictions on the use of I^{131}.

Clark & Rule (42) and McCullagh (44) list almost the same criteria they follow in selecting patients for radioiodine treatment: (*a*) uncomplicated hyperthyroidism in patients over 40 years of age; (*b*) postoperative recurrence; (*c*) severe cardiovascular disease or other complications which would increase operative risk; (*d*) failure to respond to antithyroid drugs; (*e*) patient's refusal to be treated in another way; and (*f*) presence of severe exophthalmos. Pregnancy, especially after the third month, is an absolute contraindication to the use of I^{131} since both Chapman *et al.* (54) and Hodges *et al.* (55) have shown collection of I^{131} by the fetal thyroid as early as the twelfth week of gestation.

It now seems clear that the best average dose of I^{131} to give is one which allows an uptake of about 100 μc. of I^{131} per gm. of thyroid after 24 hr. (43, 44). If a toxic adenomatous goiter is to be treated with radioiodine, and there are two schools of thought about this, much larger doses are needed. Cook (56) advises giving doses of 20 to 50 mc. to these patients. In his series he achieved good control with this dose.

With the above dose of I^{131}, most of the studies show that about 75 per cent of the patients will be controlled with one dose, 12 to 15 per cent with two doses, and the remainder with three or more. McCullagh (44) reported only two failures out of 1235 patients treated. The incidence of posttherapy myxedema varies from 8 to 20 per cent and averages about 9 to 10 per cent. True recurrence of hyperthyroidism after euthyroidism has been attained is extremely rare. The average time required to become euthyroid is 8 to 12 weeks, but in some cases radioiodine may continue to exert an effect for as long as 12 months.

Radioiodine in the Diagnosis and Treatment of Thyroid Cancer

Keston *et al.* (57) were the first to report the spontaneous uptake of radioiodine in a thyroid tumor metastasis, but it was not until 1946 that Seidlin, Marinelli & Oshry (58) were able to publish their report on the beneficial effects of I^{131} in cases of metastatic thyroid tumors. At first, there was a great wave of optimism and enthusiasm. Unfortunately, the years have produced little evidence that I^{131} is the complete answer to the treatment of thyroid malignancies. It has become clear that although I^{131} can achieve amazingly good results in some cases, this number is relatively small, and to this date there has not been a single report of a proved cure with this agent.

There have been many excellent articles written on this subject (59 to 63, 198, 199), and among the most recent and most comprehensive is the paper by Maloof (64) summarizing the experience of the group at the Massachusetts General Hospital. Once interest in this method therapy had been aroused, it soon became apparent that only a small percentage of the cases had spontaneous concentration of I^{131} in the metastases. Fitzgerald & Foote (65) showed by means of radioautographs that there is a correlation between the histology of the tumor tissue and iodine concentration—those tumors which are most similar to normal thyroid are the most likely to pick up

iodine. However, this relationship is not an absolute one, and predictions as to function based on the microscopic picture are frequently wrong. In addition, they and others demonstrated the erratic distribution of the radioiodine within a single metastasis. Thus, certain areas might get a tumoricidal dose of radiation from the isotope, but other areas would get a very much lower radiation dose.

Seidlin *et al.* (66) and Rawson *et al.* (67) were early advocates of total surgical thyroidectomy as a means of increasing tumor concentration of I^{131}. Rawson & Trunnell (60) also suggested administering thiouracil in large doses for 5 to 8 months to these patients as a means of further stimulating tumor pickup and claimed that such a program will produce some degree of function in the tumor in about 70 per cent of the cases (68). However, the amount picked up is usually not sufficient to achieve significant radiation of the tumor tissue. TSH injections have on occasion increased tumor functioning but, again, usually not to the point where therapy with I^{131} becomes feasible.

Sturgeon and co-workers (69) and Maloof *et al.* (64) have warned of the danger of stimulating the growth of thyroid metastases by the above procedures without achieving a corresponding increase in function, with disastrous consequences for the patient.

Diagnosis of thyroid cancer.—Ordinarily, isotope studies do not help in the preoperative diagnosis of thyroid malignancy. It is quite unusual for a distant metastasis to pick up iodine while normal thyroid tissue is still *in situ*. However, it does occasionally occur and is of great help in planning future therapy. In the case of solitary nodules in the thyroid gland, radioiodine studies may also be of value. Perlmutter & Slater (70, 71) and Johnson & Beierwaltes (72) have studied the uptake of I^{131} by nodules in the thyroid, by either direct counting or scanning procedures. Nodules were classified as "cold" if their uptake was very much less than a corresponding area in the other lobe, "hot" if their uptake was much higher, and "warm" if it was intermediate. There was a 30 per cent incidence of malignancy in the "cold" nodules, and no proven malignancy in the solitary "hot" nodules. There have not been enough cases studied yet to be certain of the statistics, but the results thus far are very interesting.

Treatment of thyroid cancer.—All of the reviews of the treatment of thyroid carcinoma stress the point that adequate surgery remains the fundamental treatment of the disease. For tumors localized to the thyroid gland or regional nodes, total thyroidectomy and removal of all visibly involved nodes is the treatment of choice agreed upon by all. Whether to do a radical or modified neck dissection is at this time a debatable point, with Crile and the Mayo group favoring the more conservative procedures.

There have been few scientific studies published on the value of external radiation therapy postoperatively. Pemberton & Black (73) and Hare & Salzman (74) mention this lack of objective evidence on which to base conclusions. They then proceed to state that on the basis of available statistics,

resection followed by external radiation probably gives better results than surgery alone. Although its value is questionable in those cases treated "adequately" by surgery, it is our policy to give external radiotherapy to these patients also. Everyone is agreed that for the inoperable anaplastic lesion, x-ray therapy is the only modality available.

Rawson *et al.* (62) caution against the unjustified and illogical use of radioiodine, particularly its early use in inadequate doses, which may depress uptake permanently without affecting tumor growth. They also inveigh against its use in lesions which do not concentrate iodine, or which are amenable to surgery.

For the patient with distant metastases who has already had a total thyroidectomy, I^{131} may be of value. Efforts to stimulate tumor function should be made, but the likelihood of stimulating tumor growth should also be considered. The evaluations of the I^{131} therapy of thyroid carcinoma in papers by Maloof *et al.* (64) and McDermott *et al.* (63), while inconclusive, are also quite gloomy.

Radioiodine in the Treatment of Cardiac Disease

The idea of treating angina or congestive heart failure refractory to the usual cardiac therapy by means of induced hypothyroidism is not new. Blumgart and co-workers suggested this type of treatment in 1933 (75), but neither surgical thyroidectomy nor the later use of the antithyroid drugs was particularly successful. In 1955, however, Blumgart *et al.* reported (76) on the results of a co-operative study in which 1070 euthyroid cardiac patients were made hypothyroid by means of radioactive iodine. These patients were severely incapacitated by their heart disease but were stable in the sense that their disability was not rapidly getting worse. Ten to twenty millicuries of I^{131} were given weekly for three doses, and then additional amounts as needed were given at one to two month intervals until frank hypothyroidism resulted. In a few cases, when larger doses of I^{131} were given (i.e., 40 to 50 mc. at one time), an exacerbation of the cardiac symptoms appeared, and one or two deaths resulted. Blumgart reported "worth-while improvement" in 75 per cent of the patients with angina and in 60 per cent of those with intractable congestive failure. Jaffe and his group have also reported on the results of treatment in a smaller series of cases, with similar results (77).

I^{131} thyroidectomy is also being used in cases of severe pulmonary insufficiency, based on the concept that reducing the metabolic rate would reduce the need for oxygen and the rate of production of CO_2 and, therefore, relieve the dyspnea. Although the results thus far are encouraging, not enough cases have been treated as yet to draw any conclusions.

Other Uses of I^{131}

The most common diagnostic application of I^{131}, aside from its use in disorders of the thyroid gland, is in the measurement of blood and plasma

volume. Since the work of Storaasli and his co-workers (78, 79), many reports have appeared attesting to its simplicity and accuracy. In this procedure, human serum albumin iodinated with I^{131} is used. The radioiodine is firmly bound to the albumin, and when the compound is injected intravenously, there is no transfer of activity to the other plasma proteins or to the red cells. There is only a very slow leakage of the iodinated albumin from the vascular tree, whereas Evans blue (T-1824) diffuses quite rapidly from the circulating plasma, and repeated determinations of plasma volume within short time intervals are not possible. Lipemia or hemolysis will interfere with the Evans blue method, but since only radioactivity is measured in the method under discussion, color or turbidity is not troublesome.

A known amount of activity, as I^{131}-labeled albumin, is injected intravenously, and after thorough mixing has occurred, a sample of blood is withdrawn and the activity of an aliquot of plasma or heparinized whole blood is measured. Using the classical dilution formula, the plasma or blood volume may then be calculated. Recently, Zipf, Webber & Grave (80) and Inkley, Brooks & Krieger (81) have published comparisons of the radioiodinated serum albumin and Evans blue methods, and both groups found excellent agreement between the two tests.

It has been reported that in patients with cardiac edema, I^{131}-albumin blood volumes were larger than those determined by labeled red cell techniques (82), and it was thought that this resulted from excessive loss of albumin from the intravascular space. Moir, Pritchard & Ford (83), using a technique which gave a continuous recording of the activity present in an artificial arteriovenous fistula, demonstrated that (*a*) in cardiac edema, mixing times were much prolonged, and (*b*) disappearance slopes for blood radioactivity were the same in edematous and nonedematous subjects. Thus, they concluded that premature sampling, before complete mixing had occurred, gave falsely low values for the labeled cell techniques and that the values for the albumin method were not too high.

Pritchard *et al.* (84) described a technique for measuring cardiac output, using I^{131}-labeled albumin and a recording scintillation counter which measured the activity in arterial blood flowing past the crystal in a steel tube. This method gave values which were in fairly close agreement with those determined by the Fick principle but obviated the need for cardiac catheterization and gas analyses. Recently, Huff (85) described an improvement whereby even the arterial puncture can be eliminated. His group found that after the intravenous injection of radioiodinated albumin a well shielded counter placed over the left parasternal line between the first and second ribs gave curves which were very similar to those obtained by Pritchard, and the cardiac outputs calculated from them were almost the same as those obtained by the Fick method.

Radioactive human serum albumin has also been used to study the status of the circulatory system in the limbs, and Shipley & Clark (86) have used NaI^{131} to measure circulation times. They used an antecubital vein for the

injection site, and the femoral artery as a counting area. Their radioactivity circulation times were about 25 per cent lower than the Decholin times in patients with congestive heart failure.

Radioactive diiodofluorescein was first used by Moore in 1948 in the diagnosis and localization of brain tumors (87). Since then, NaI^{131} and I^{131}-labeled human albumin have also been used for this purpose (88, 89). The localization of the radioactivity at the tumor area is not really attributable to a specific concentration of these substances by the tumor tissue but rather to a disruption of the blood/brain barrier at the tumor surface. This discontinuity allows leakage of certain anions from the blood vessels. Since the concentration factor is relatively low and since precise localization is desired, special counting methods are usually employed. Allen & Risser (90) have recently described such a device which combines the features of a well shielded and collimated scintiscanner with a pulse-height analyzer.

Yuhl & Stirrett (91, 92) have used radioactive iodinated serum albumin to diagnose the presence or absence of liver metastases. They scanned the abdomen after an intravenous injection of I^{131}-albumin and found that the I^{131} localized in the liver region in cases with metastases or liver abscess. Ascites, active peptic ulcer, or inflammatory processes in the liver gave occasional false positive results. A diagnostic accuracy of 90 to 95 per cent is claimed for this technique. These same authors have also attempted to do myeloscintograms, injecting the iodinated albumin into the spinal canal and scanning with a scintiscanner (93). Although the albumin may be less irritating than iodized-oil contrast media, the scintigrams published are not as satisfactory as the standard myelogram.

A very promising use of I^{131} was revealed by Taplin *et al.* in 1955 when they described the radioactive Rose Bengal test of liver function (94). The Rose Bengal dye is made radioactive with I^{131}. Following its intravenous injection, it is cleared from the blood by the polygonal cells in the liver and then secreted into the bile. By placing a counter over the liver area and then giving the dye, curves are obtained of the build-up and then decrease of activity in the liver. Parenchymatous liver disease is said to give a curve distinctively different from extrahepatic obstructive jaundice. Since the measurement is unaffected by icterus, it should be of value in those cases where the Sulfobromophthalein test cannot be used.

Radioactive Phosphorus

Diagnostic uses.—The labeling of red blood cells with radiophosphorus (P^{32}) and their use in the measurement of blood volume and red cell volume were first described by Hevesy. If red blood cells are incubated with $Na_2HP^{32}O_4$ at 37°C. for 1 hr., about one half of the available P^{32} will become bound to the trioses and hexoses of the red cells (95, 96). After washing with saline to remove free P^{32}, an aliquot of resuspended P^{32}-labeled red cells is injected and 10 to 15 minutes later, a blood sample is drawn. After comparing the activity of the cells in the 15 min. sample with an equal volume

of the cells which were injected, one may calculate the red cell mass by means of the dilution formula (128). Although the red cells do not normally penetrate the endothelial barrier, they do lose about 6 per cent of the label per hour, and thus only short-term studies are possible. In many institutions, red cell mass is now measured by means of radiochromium tagged cells, primarily because of the ease in counting the latter. P^{32} emits only beta particles, and the samples must be processed before counting in a Geiger counter. The gamma photons from Cr^{51} permit its measurement in the much more convenient well-type scintillation counter.

P^{32} has also been used to locate brain tumors. Since the beta particles do not penetrate the skull, tumor localization with P^{32} necessarily is done at the operating table, after the skull has been opened. P^{32} (300 to 500 μc.) is given intravenously either before or during the operation, and the suspected area explored with a needle-like Geiger counter first used by Selverstone and co-workers (97). Selverstone and others have found the procedure useful in delimiting the margins of the tumor and in determining the completeness of its removal. For preoperative diagnosis and localization, radioiodine-labeled albumin is used, and more recently, the positron-emitting isotopes such as arsenic[74] (98). Amyes *et al.* (99) and Garrity & Matthews (100) reviewed this subject recently, and both found the P^{32} procedure to be of definite value.

P^{32} is of questionable value in locating breast or skin carcinomas. The uptake of P^{32} depends in part on the turnover rate of stable phosphorus in the particular tissue studied. Since most neoplasms have a high rate of metabolic activity, it was soon found by Lawrence and his co-workers that P^{32} concentrated in tumor or leukemic tissues (101 to 104). Reasoning from this, it was thought that the degree of malignancy of superficial lesions could be ascertained by measuring their uptake of P^{32}. Breast abscesses gave the same degree of P^{32} concentration as carcinomas. Bauer & Steffen reported on this method of differentiating benign from malignant skin lesions (105). They found that although malignant melanomas gave a significantly higher counting rate than normal skin after the intravenous injection of P^{32}, basal and squamous cell carcinomas could not be distinguished from benign skin lesions with any degree of accuracy.

Therapeutic uses.—P^{32}, the first artificially produced radioisotope to be applied in therapy, was used by Lawrence in 1936 in the treatment of chronic leukemia (106). Because of its concentration in tumor tissue, and therefore its possible use for selectively irradiating the tumor, radiophosphorus has been used in the therapy of many types of neoplasia. Excellent results have been obtained in polycythemia vera, chronic leukemia, and giant follicle lymphoblastoma. It is occasionally of value in multiple myeloma (107) and in lymphosarcoma. It has usually been of little value in other types of neoplasia. Since P^{32} eventually localizes the bone marrow, the danger of depressing hematopoiesis limits the radiation dose that can be delivered to tumor tissue by this method.

The first example of a disease successfully treated and controlled with artificially produced radioactive isotope is polycythemia vera (106, 202 to 206). In our series of 263 cases, once a satisfactory remission is obtained, the average interval before treatment is needed again is 33 months (108). Stroebel & Hall reported average remissions of 18 to 24 months in their patients (109). After an initial dose of 3 to 5 mc., the blood count usually falls, beginning about one month after therapy. The platelet count is reduced first, followed by a decrease in the white count and later by a fall in the hematocrit. After three months, the need for a second dose of P^{32} and its size are estimated by the clinical and hematological response to the first.

Lawrence (108) reported a mean survival time of 13.3 years in his series of 263 cases, as compared with 6.7 years for a group of patients who were not treated with radiophosphorus, reported by Videbaek (110). Stroebel & Hall (109) feel that the incidence of acute leukemia may be increased in P^{32}-treated cases, but absolute proof is lacking. Wiseman *et al.* (111) published a report on their cases, and it was their opinion that the number developing chronic leukemia has markedly decreased. It may be that the development of leukemia in a patient with polycythemia vera is not a complication of treatment but a manifestation of the natural course of the disease (112, 207). Nevertheless, the extension of the survival time which has resulted from treatment with P^{32} is a remarkable achievement and compares with the results achieved in diabetics after the discovery of insulin, and in patients with Addisonian anemia after the onset of parenteral liver therapy.

P^{32} has little place in the treatment of acute leukemia, but it is sometimes of value in cases with marked hyperplasia. Small doses are used. P^{32} has been effective in the treatment of chronic leukemia. Our cases of chronic lymphatic leukemia, treated with P^{32}, have a median survival time of 5.4 years, and the chronic myelogenous group has a median survival time of 3.2 years (113). These are better than any previously reported, although the increase in survival in the myelogenous group is not striking. After early experiences with the administration of relatively large single doses of P^{32}, we learned that because of bone marrow damage, it is not possible to eradicate leukemic tissue with P^{32}. Consequently, since 1940 we have used P^{32} in intermittently administered small doses anticipating any activity of the disease (113).

Tivey carried out an elaborate statistical study of 1978 cases reported in the literature from 1925 to 1951 (114). His conclusions are interesting in that he too found a significant extension of life with P^{32} treatment. Osgood, Seaman & Tivey, using similar statistical methods, found that the treatment of patients with chronic leukemia with small intermittent doses gave better results than standardized conventional courses of treatment (115).

Many years ago the present authors used intravenous or oral P^{32} in an attempt to treat carcinoma of the breast or prostate metastatic to bone (116, 117) without very encouraging results other than the control of pain in some instances. Friedell has also reported a series of patients so treated

(118). In the treatment of giant follicle lymphoblastoma, P^{32} has produced results which seem to prove its value in this condition (117, 119).

Colloidal chromic phosphate containing P^{32} was first used by Jones, Wrobel & Lyons as a means of irradiating the reticulo-endothelial system (120). Since 1942 we have been using this colloidal material intravenously for the treatment of splenomegaly and hepatomegaly attributable to neoplastic or leukemic invasion, by local infiltration into lymph node metastases, and intraperitoneally and intrathoracically for ascitic and pleural effusions (117). Jaffe and his group have recently reported on the use of this material in the palliative treatment of serous effusions secondary to malignancies and in the treatment of certain tumors by interstitial infiltration (121, 122). Chevallier and Burg have also used colloidal chromic phosphate interstitially (208). Their reported results are comparable to those obtained elsewhere with colloidal Au^{189}. They list several technical advantages of the P^{32}-chromic phosphate as compared with radiogold. Chief of these are (*a*) its longer half-life, and hence less loss of activity in shipment, and (*b*) the absence of gamma radiation, which reduces the personnel protection problem and permits the use of lighter and less awkward equipment. Whether it really is more effective than radiogold remains to be seen, but some workers feel that the gamma component of the Au^{198} radiation is valuable in irradiating all areas of a tumor and not just those adjacent to the injection site.

Radioactive Gold

Radiogold (Au^{198}) is used medically in the form of a colloidal dispersion, the particles of which range in size from 0.003 to 0.007 μ. Because of its particulate nature, like colloidal chromic phosphate, it is not absorbed into the body fluids or circulation but is phagocytosed or adsorbed on the surfaces of cells. It emits beta particles with a maximum energy of 0.9 Mev and an average range in tissue of 0.7 mm. It also decays by gamma emission, and the photon has an energy of 0.4 Mev.

Radiogold is used only for therapeutic purposes and, most commonly, in the treatment of malignancies by either intracavitary injection or interstitial infiltration.

Intracavitary use.—Goldie & Hahn demonstrated in 1950 that viable tumor cells in the peritoneal fluid of rats failed to implant and grow if colloidal radiogold in sufficient dosage was injected into the serous cavity (123). Since that time, extensive use of this material has been made in patients with serous effusions secondary to malignancies. Recent review articles have been written by Seaman, Sherman & Bonebrake (124), Simon (125) Moses, Kent & Boatman (126), Müller (209), Neukomm (210), and others. In general, most of the reports are similar in stating that (*a*) fluid accumulation is stopped or reduced in 40 to 60 per cent of the patients, (*b*) there is little real evidence of increased survival following this type of therapy, (*c*) there are few reactions or complications of the treatment other than mild radiation

sickness, and (*d*) the exact mechanism by which Au^{198} slows down serous surface effusions is still not known.

Doses used have been between 50 to 100 mc. of the colloidal radiogold per pleural space and 75 to 150 mc. in the peritoneal cavity. Very little is absorbed into the blood stream.

Recently several groups have been instilling radiogold into the peritoneal cavity if there is any question of tumor seeding or small implants after surgery. It is still too soon to evaluate the efficiency of this possible prophylactic use of Au^{198}.

Interstitial infiltration.—Since 1942 radioactive colloids (chromic phosphate) have been directly injected into tumor masses for a localized radiation effect. More recently colloidal gold has been used also (127). It has been used most frequently in treating carcinoma of the prostate which has invaded the capsule of the gland. Radiogold is injected throughout the substance of the gland, either through the bladder after a cystostomy has been done, or through the perineum. Caution must be exercised in either case, since infiltration of the rectal wall or excessive radiation to it may result in rectal ulcerations and fistulae. About 1 to 2 mc. are injected per gm. of prostatic tissue with a maximum dose of 150 mc.

At first, infiltration alone was used, but the results were not very good. Even with the gamma radiation from Au^{198}, it is almost impossible to get a uniformly tumoricidal dose of radiation when it is infiltrated in this manner. Kerr and his group now recommend the surgical removal of as much tumor tissue as possible and then infiltration of the remaining tumor with the colloidal gold (128, 129). Rounds & Evans (130) have devised a method for monitoring the blood during the infiltration so that an excess does not get into the blood and away from the tumor site.

It must be emphasized that the value of radiogold infiltration of the prostate still remains to be proved. Huggins has reported significant prolongation of survival in his patients treated by a variety of antiandrogenic procedures [orchiectomy, adrenalectomy, estrogenic hormones, etc. (131)]. It is our opinion that in the selection of cases for treatment with Au^{198} these other therapeutic measures should also be considered.

Hinman *et al.* (132) have reasoned that if colloids are picked up by phagocytic cells and transported via the lymphatics, then presacral space injection of radiocolloids should irradiate the retroperitoneal nodes. Their data reveal that large deposits in the presacral space are carried to most or all of the retroperitoneal nodes. Smaller ones may be limited to the iliac nodes, however. Particle size influenced the rate of removal and spread. The effect of particle size on distribution of colloids has been extensively studied by Gofman and associates (133, 134).

Allen and his group have been treating cervical carcinomas by "parametrial" infiltration with radiogold (135). Their results thus far are encouraging but not conclusive.

Radioactive Iron

Radioiron (Fe^{59}) which emits both beta particles and gamma photons, may be counted by means of the scintillation counter, and this permits ready localization of its activity by body surface counting. There have been no therapeutic applications using Fe^{59} as yet, but since the work of Huff *et al.* (136, 137), it has proved to be of great value in the diagnosis of many hematologic disorders, particularly those involving the red blood cell.

Much information has been gained about the metabolism of iron and hemoglobin using Fe^{59}. Granick wrote an excellent review of the basic physiology of iron (138) as has Hemmeler (211). Huff and his co-workers at the Donner Laboratory, using Fe^{59}-citrate, were able to bind the iron to globulin, and by injecting the tagged iron-globulin complex, studied the blood volume and plasma and red cell iron turnover in normal subjects and in patients with various types of anemia (136). The value of these studies in the diagnosis of obscure anemias was greatly increased when, in addition to the blood volume and plasma and red cell iron turnover data, *in vivo* measurements over the liver, spleen, heart, and sacrum (to represent bone marrow) were added to the study (137, 139). Not only could a dynamic picture then be obtained of the movement of iron in and out of the red cells and plasma, but its actual tissue localizations could be discovered. It was reported that in patients with untreated polycythemia, pernicious anemia in relapse, chronic leukemia, hemolytic or iron-deficiency anemias, and erythroid hyperplasia, the iron turnover was increased. Decreased iron turnover is seen in patients with erythroid hypoplasia, marrow arrest at a stage prior to the incorporation of iron into the red cell, or aplastic anemias (139). By studying the plasma iron turnover together with *in vivo* body counting, one can easily distinguish splenomegaly with extramedullary hematopoiesis from splenomegaly with active red cell destruction. In the ordinary aplastic anemia, there is usually a decreased rate of disappearance of iron from the plasma and an increased uptake in the liver. Some patients have the peripheral blood picture of an aplastic anemia but have a hyperplastic bone marrow. In these individuals, there is usually a rapid clearance of iron from the plasma into the marrow, where it remains for a short time and then accumulates in the spleen (splenic destruction of abnormal cells).

There have been many publications on the general subject of erythropoiesis or erythrokinetics, and among the more recent are the studies by Bothwell *et al.* (140), Giblett *et al.* (141), Wuhrmann & Jasinski (212), Badenreh & Callender (213), and Pollycove & Mortimer (142). In this last paper, the authors set up a five-compartment model for the movement of iron and solved the corresponding differential equations to obtain the intercompartmental rate constants. A surprising finding was the disclosure that the interchange from marrow to plasma was much larger than the plasma-liver/spleen exchange. By means of the mathematical model and the radioiron turnover data, a quantitative estimate of hemoglobin synthesis was obtained.

Hoag *et al.* (214) have used Fe^{59} tagged red cells to measure activity appearing in the feces of infants with iron-deficiency anemia. Although inadequate diet, faulty absorption, and decreased prenatal stores of iron may contribute to the development of the anemia, they consider blood loss a major etiologic factor. Fe^{59} has also been used to study iron absorption in patients with iron-deficient anemia who do not respond to oral iron therapy (215). It is now possible to measure red cell life span simultaneously with other radioiron studies. Consequently, with a single isotope, it is possible to estimate the rate and site of red cell production and destruction and the duration of life of the red cell (143).

The use of Fe^{59} as described originally by Huff is now becoming a standard laboratory procedure for the study and diagnosis of problem anemias in many hospitals, clinics, and laboratories.

Radioactive Chromium

Radiochromium (Cr^{51}) is another gamma emitter which is proving to be exceedingly valuable in hematology. By a procedure similar to that for labeling cells with P^{32}, Cr^{51} can be introduced into the red cells, where it becomes tightly bound to hemoglobin. After the unbound $Na_2Cr^{51}O_4$ is reduced by ascorbic acid, the labeled cells may be used exactly as the P^{32}-tagged cells, in the measurement of total red cell volume (144, 145). There have been many comparisons of the two methods published, and in all, the two methods give almost identical results (146). Since the Cr^{51}-labeled cells may be counted in a vial in a well-type counter, the counting procedure is somewhat easier than with P^{32}. The label is exceedingly stable, less than 1 per cent being lost daily as a result of elution from the cells. Kurtz & Tivey emphasize that because of this, only the intravascular space is measured, and if no blood is lost, repeated determinations of red cell mass can be made within a 24 hr. period after injection of the cells (147).

Cr^{51}-tagged cells may also be used for red cell survival studies, and the measurement is much easier to do in this manner than by the Ashby technique (148). This method does not give an exact measure of the red cell life, but the data can be used to determine whether a shortened red cell life is present by comparison with the data found for normals by this method. A patient's cells may be autotransfused or injected into a normal individual, or normal tagged cells may be transfused into the patient and their survival studied. In this way, abnormalities of the patient's cells may be uncovered, or a nonspecific hemolytic process may be revealed. Sprague & Paterson (149) have studied the half-survival times in normal subjects and in patients with hemoglobinopathies. Normal individuals had half-times averaging 27 days, whereas in sickle cell disease and sickle cell-hemoglobin C disease, the values were much shorter. This was true when the cells were given to normal recipients or autotransfused.

Strumia *et al.* (150) emphasize that whereas Cr^{51} survival studies are valid when tagged cells are injected into a normal recipient, they are not

when the recipient's red cell mass is changing. There is an underlying assumption that the total red cell mass is constant, with the rate of red cell formation equaling the rate of red cell destruction. If the red cell mass is falling (if hemolysis or hemorrhage exceeds capacity for red cell formation) or rising (as in the recovery phase after hemorrhage or hemolysis), this equilibrium is not present, and a correction must be made. This can be done if frequent estimations of total red cell mass are made.

Cr^{51}-labeled cells are also used to measure the viability of stored erythrocytes. An aliquot of the stored cells is tagged just before transfusion into a normal, and their survival can than be easily followed.

Jandl *et al.* studied the fate of the red cells labeled with Cr^{51} (151) as had previously been done with Fe^{59} (139). They autotransfused radiochromium-labeled cells and then measured the activity in the blood and did *in vivo* body surface counting over the spleen and liver. Progressive accumulation of Cr^{51} in the spleen accompanied the disappearance of Cr^{51}-tagged cells from the circulation, indicating active red cell sequestration in the spleen. Thus, with another isotope, further information on red cell formation and destruction can be obtained.

However, although Cr^{51} can be used for cell survival studies and for estimating some of the aspects of the dynamics of red cell production and destruction, we feel that much more information can be obtained using Fe^{59}. Red cell production and hemoglobin synthesis can be studied only with the iron isotopes. We therefore prefer to study our problem anemia patients with iron^{59}, since a more detailed and comprehensive picture of their hematologic status can be obtained with this isotope.

Radioactive Cobalt

Radiocobalt (Co^{60}) has several interesting applications in medicine. When properly shielded, its radiation spectrum is almost the same as that of radium (152, 153). Its moderately long half-life and ready availability and the ease of machining it into various shapes have stimulated research into its clinical use as a substitute for radium. It has been used in the form of needles for interstitial therapy and as spheres or as a solution for intracavitary applications.

Cobalt^{60} is also being widely employed as a radiation source in teletherapy units (154, 155, 156, 216). Since an almost monoenergetic beam is obtained from a cobalt source, filtering (and its consequent reduction in beam intensity) is not needed. The maximum radiation dose is not at the skin, but about 6 mm. below it, and it is hoped that skin reactions will be less troublesome with this form of radiotherapy. Only a simple holder and shield are needed, and these are much less expensive and more maneuverable than comparable high-voltage x-ray units. One cannot expect remarkable results from such use of Co^{60}, however. It is simply another source of high energy radiation, which should give as good results as high voltage and supervoltage

x-rays in cancer therapy. It is doubtful whether any real improvement in survival will result.

Cobalt^{60} is also being used widely in one tracer application. In the form of Co^{60}-labeled vitamin B_{12} it is being used as a test of intrinsic factor activity. Chaiet, Rosenblum & Woodbury reported the first synthesis of B_{12} containing Co^{60} (157). Using this substance Heinle proposed a test in which he measured the fecal excretion of a small oral test dose in normal subjects and in patients with pernicious anemia (158). Patients with pernicious anemia excreted 85 to 95 per cent of the activity given them, and normal individuals excreted only 15 to 40 per cent. Then Schilling devised a test whereby he could measure intestinal absorption of the labeled vitamin by measuring the urine excreted in the 24 hr. period following ingestion of the test dose (159). He gave a small oral dose of the radioactive B_{12} and shortly thereafter flooded the body with an injection of 1000 μg. of nonradioactive vitamin B_{12}. Since the body's stores were presumed to be saturated with this massive dose, he reasoned that the labeled vitamin, if absorbed, should appear in the urine, and such indeed was the case. Normal subjects excreted 1.5 to 5.3 per cent, and pernicious anemia patients excreted 0.0 to 0.65 per cent. In 1954 Glass *et al.* (160) published their modification wherein they measured the amount of activity detected by a scintillation counter placed over the liver area after an oral dose of the Co^{60}-labeled vitamin. Pollycove & Apt have recently published an evaluation of all three tests and reported that they correlate well with each other (161).

This test is extremely useful in establishing or ruling out the diagnosis of pernicious anemia in patients with gastric anacidity who have already been treated with liver or vitamin B_{12} for a macrocytic anemia. Since the absorption of the test dose of vitamin B_{12} depends only on enough intrinsic factor being present, previous therapy will not influence the results, provided a source of intrinsic factor is not given prior to the test. By the same token, it is a very rapid and accurate way to assay the potency of intrinsic factor preparations. Patients with known Addisonian anemia are used, but they can be treated and in remission, and the test will still be valid. In addition, results are obtained much sooner than in the method of observing the degree of reticulocyte response obtained, and the same patient can be used as an assay instrument much more frequently (if the liver is blocked by the flushing dose).

Miscellaneous Uses

Since this review will cover only isotopes of clinical interest, the vast body of literature concerning the research applications of the radioisotopes will not be discussed. Carbon^{14}, hydrogen^{3}, sodium^{24}, potassium^{42}, and many others are being used in ever increasing amounts in research laboratories all over the world and are helping to answer many questions in biology and medicine which could not be investigated without radioisotopes. For example, extensive studies of red cell life have been carried out with C^{14}-

labeled glycine (162, 163), and H^3, or tritiated, water is being used to measure total body water (164). Body water determinations can now be carried out on a routine basis in the office, laboratory, or clinic, and these are of value in the management of patients with edema (165, 217).

Two relatively uncommon but interesting uses of the isotopes will be mentioned before closing, however. In brain tumor localization, one of the main problems is to improve the resolution of existing scanning methods so as to more accurately pinpoint the lesion. Wrenn, Good & Handler developed a method for tumor localization using positron-emitting isotopes instead of I^{131} or P^{32} (98). A positron is a particle similar to the electron, but with a positive instead of negative charge. In its interaction with matter, a positron eventually collides with an electron, and both are "annihilated." Simultaneously, however, two gamma photons are emitted, each with the same energy as the other but traveling in exactly opposite directions. This idea of using a space-oriented radiation was subsequently developed by Brownell & Sweet (166). They gave the patient arsenic^{74}, which is a positron emitter, and then counted the activity in the head using two scintillation counters with very narrow apertures, one on each side of the head and each directly facing the other. Counts were recorded only when photons entered the two counters simultaneously (coincidence counting). Much better resolution was obtained in this way than by any previous means.

Finally, mention should be made of the only human exposure thus far given at an atomic reactor. Boron concentrates in brain tumor tissue, its concentration there rapidly approaching the blood level of boron. Normal brain tissue does not do this, but eventually, blood, tumor, and normal brain tissue do equilibrate and have equal concentrations of boron. Boron^{10}, which is a stable element, has a high affinity for slow or thermal neutrons. When they interact, an unstable compound nucleus is formed, which breaks down into lithium and alpha particles and gamma photons. This release of radioactivity at the site of boron concentration in tumor tissue offered the possibility of selectively irradiating the tumor. Early experiments by Kruger in this laboratory (167) demonstrated radiation effects in animal tissue by this method. Based on this work human brain tumor exposure has been carried out by Farr *et al.* at the Brookhaven National Laboratory (168, 169). Patients with glioblastoma multiforme were given intravenous injections of B^{10} (as borax) and then put in the slow neutron flux of the research reactor there. Although the results have not been dramatic, they were encouraging and work is still progressing on this project. So far, insufficient dosage in terms of roentgens delivered to the tumor is the problem.

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CONNECTIVE TISSUE (COLLAGEN) DISEASES[1,2]

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Introduction

The term "collagen disease," originated by Klemperer and his associates in 1942 (5), was designed to include principally systemic lupus erythematosus (SLE), systemic scleroderma, rheumatic fever, rheumatoid arthritis, polyarteritis nodosa, and dermatomyositis. Eight years later Klemperer wrote,

> I believe today that even this cautious synthesis was premature because it resulted in an indiscriminate acceptance of a term with a diagnostic and pathogenetic import not originally intended when it was conceived. A peculiar worship of diagnostic terms has led to an exaggerated popularity of the diagnosis collagen disease. There is danger that it may become a catch-all term for maladies with puzzling clinical and anatomical features (6).

Since collagen is but one constituent of connective tissue and since, moreover, the other major component, ground substance, may play an even more important role in the pathogenesis of these disorders, the term "connective tissue diseases" would seem more appropriate. All the diseases enumerated by Klemperer were included in this review, with the exception of rheumatic fever.

General

The strongest link which binds together the various connective tissue diseases is a common histopathologic pattern: an increase in interfibrillary ground substance, a proliferation of fibroblasts, an inflammatory reaction distinguished by the presence of mononuclear cells, and necrosis associated with deposition of fibrinoid material. This type of reaction is characteristic of the connective tissue response to injury (7). The cardiovascular structures

[1] This review was completed September 1, 1956. Attention was given principally to papers that were published from 1950 to 1956. No attempt was made to append an exhaustive bibliography. In the sections that follow, worthwhile reviews have been cited both for the convenience of the readers and as an expedience to the writers of this chapter. Special mention should be made here of the exhaustive "Rheumatism Reviews" by the Editorial Committee of the American Rheumatism Association (1, 2), the scholarly review on systemic lupus erythematosus integrated with a detailed analysis of 138 observed cases by the Johns Hopkins group (3), and the comprehensive monograph on Collagen Diseases by Talbott & Ferrandis (4). These four references have been found especially useful and are warmly recommended to the reader.

[2] The following abbreviations are used in this review: DNA (desoxyribonucleic acid); LE (lupus erythematosus); SLE (systemic lupus erythematosus).

TABLE I

TISSUE CHANGES CHARACTERISTIC OF THE CONNECTIVE TISSUE DISEASES*

	Increased Ground Substance (or Edema)	Fibroblast Proliferation	Inflammatory Reaction (Mononuclear)	Fibrinoid Necrosis	Occurrence of		
					Vasculitis	Endocarditis	Pericarditis
Rheumatoid Arthritis Subcutaneous Nodules Synovitis	 ++ ++	 +++ +++	 +++ ++	 +++ +	+	+	++
Rheumatic Fever Subcutaneous Nodules Aschoff Body Valvulitis	 ++ + +++	 +++ + +	 +++ +++ +	 + + +++	+	+++	+++
Polyarteritis Nodosa Adventitia Media Intima	 + 0 +	 +++ + ++	 +++ + ++	 + +++ ++	+++	0	0
Dermatomyositis	+	++	++	+	+	0	0
Lupus Erythematosus	++	0†	0†	++	++	++	++
Scleroderma	++	+ (Fibroblast) +++ (Collagen)	0	0 (Skin) + (Vessels)	+	0	0

* The number of plus signs indicates frequency and/or degree of severity. Although rheumatic fever is not discussed in the text it is included in the table for comparison.

† Fibroblast proliferation (+) may be seen in kidney, skin and synovial tissue. Cellular infiltration (+) may be present in myocardium, skin and synovium.

are commonly affected. Thus vasculitis, and less consistently endocarditis and pericarditis, accompany the alterations seen in these diseases. The tissue changes observed in connective tissue diseases are summarized in Table I. Attention is drawn to the fact that the inflammatory response is much less prominent in systemic lupus erythematosus and scleroderma than in the other conditions (7).

In addition to the pathologic changes, there are many clinical features that these diseases share in common. Symptoms resulting from involvement of many organs and structures attest to the systemic nature and widespread distribution of the morbid processes. Structures that are especially vulnerable include those lined by endothelium (blood vessels, endocardium), mesothelium (pericardium, pleura, and peritoneum), synovium and the tissues of the eye. It is noteworthy that in each of the connective tissue diseases one may encounter, clinically, localized or systemic forms. The latter may be malignant or fulminating and generally portends a grave prognosis.

Since 1949 a third common bond has become evident; namely, the prompt clinical response that follows administration of corticotropin or 11,17 oxygenated steroids. There is universal agreement that, whereas, these hormonal agents alter host-cell response, suppress inflammation, and often control the most striking and debilitating symptoms, they are, nevertheless, not curative, do not eradicate the causative agent, do not induce a remission (although the patient may be tided over, and permanent tissue damage reduced, until a remission supervenes) and most likely do not alter significantly the ultimate course of events. Yet, it has been repeatedly observed that these steroids are life-saving or life-prolonging.

Careful consideration has been given by numerous workers to the etiology of the various connective tissue diseases and many attempts have been made to reproduce some of these diseases in experimental animals. Polyarteritis, histopathologically indistinguishable from that seen in man, has been produced in rabbits rendered hypersensitive to horse serum (8). Indeed, numerous cases, although still a small percentage, of polyarteritis in man resulting from hypersensitivity to a number of diverse drugs were reported. Nevertheless, the etiology of the human connective tissue diseases here considered remains unknown and the pathogenesis obscure. Unknown cause may thus be cited as a fourth feature (albeit a negative one) that the connective tissue diseases have in common.

Physico-chemical composition and metabolism of connective tissue.—The structure, origin, chemical composition, biosynthesis, function and metabolism of the connective tissue components are being actively investigated at present in many laboratories. Even recent concepts are being revised as newer knowledge and clearer insight are gained by employment of more sophisticated methods, instruments of greater precision, and experiments of imaginative design.

Connective tissue consists of cellular and extracellular (fibrous) structures embedded in a matrix of amorphous ground substance through which

pass water, electrolytes, protein and other substances in transit between blood and parenchymal cells. The ground substance may also store water and electrolytes. The cells consist principally of fibroblasts, fibrocytes and macrophages. The fibrous structures are composed mainly of collagen and to a lesser extent of elastic and reticulin fibers. Three forms of collagen have been distinguished chemically on the basis of extraction procedures: alkali-soluble collagen (probable precursor of collagen fibrils); acid-soluble collagen (formerly considered "procollagen"); and insoluble or "mature" collagen (9).

The constituents of the ground substance that have received the greatest attention during the past two decades are the mucopolysaccharides. These are high molecular weight polymers formed from amino sugars (hexosamines) in combination with glucuronic acid that exist in loose association or complex with proteins (10, 11). Two connective tissue mucopolysaccharides that have been most intensively studied are hyaluronic acid and chondroitin sulphate. Recently additional mucopolysaccharides have been characterized: chondroitin sulphate A, B and C, chondroitin, and keratosulphate (12). The chondroitin sulphates have a high negative surface charge and hence, marked cation and water-binding capacity (10, 13).

Studies on metabolism of mucopolysaccharides did not begin to attain substantial dimensions until around 1950. It has been established recently that chondroitin sulfuric acid in cartilage originates from cartilage cells, and that hyaluronic acid is synthesized by fibroblasts (14). The most promising contributions to our current and still preliminary knowledge of the intermediary metabolism of these polymers derive from a definition of the enzyme systems that catalyze formation of mucopolysaccharides and from an elucidation of the pathways and rate of biosynthesis. Comprehensive reviews of these significant advances have appeared recently (9, 10, 12, 13).

Systemic Lupus Erythematosus

Three important advances have been made during recent years: development of a dependable diagnostic test, discovery of therapeutic agents which effectively control the acute, systemic symptoms and acquisition of a better understanding of the natural history of this disease.

The LE cell phenomenon.—The serum or plasma of patients with SLE contains a substance which, *in vitro*, is responsible for the alteration of the nuclear material of normal leucocytes. This material may then become engulfed by polymorphonuclear cells or monocytes and appear on Wright-stained smear as a homogeneous red-purple inclusion body (LE cell). Several modifications of the technique for demonstrating the LE cell have been described (15). The LE factor is associated with gamma globulin and localized in Cohn Fraction II. It has been suggested that this factor acts by releasing desoxyribonuclease from its normally occurring inhibitor, thus permitting the enzyme to depolymerize desoxyribonucleic acid (DNA) (16).

The LE factor has been found not only in plasma but also in urine, cerebrospinal, pleural and pericardial fluids. Since LE cells are not present in direct (non-incubated) smears of peripheral blood or bone marrow of patients with lupus, formation of such cells appears to be an *in vitro* phenomenon. Other workers, however, have drawn attention to the identical morphological, tinctorial and histochemical properties of the LE cell inclusions and the hematoxylin-staining bodies found at necropsy in tissues of patients with SLE (6). The LE cell test has been found positive in about 82 per cent of patients with SLE. Controversy exists, however, as to the specificity of this test. Some authors (17, 18) have reported false-positive reactions in a variety of unrelated diseases; nevertheless, very competent students of this disease have searched for LE cells in over 2,000 cases of numerous diseases other than SLE (including other collagen diseases) and have failed to find unequivocally positive reactions (3, 19, 20). Of special interest, however, is a small group of patients with hypertension who developed clinical symptoms of SLE and positive LE cell tests after prolonged hydralazine therapy. The clinical features and the LE phenomenon disappeared after hydralazine was discontinued.

Anticipation of SLE by serologic test for syphilis.—It had been noted repeatedly that serum of patients with SLE quite frequently (17 per cent to 35 per cent) gave a positive reaction for syphilis (21). Recently the intriguing observation was reported (22) that 42 per cent of a group of 148 subjects, found to have on routine examination a chronically positive serologic test for syphilis, but a negative treponemal immobilization test (hence a false biologic positive test for syphilis), developed during the course of subsequent years either SLE, "collagen vascular disease," or rheumatoid arthritis. It thus appears that changes in serum protein may precede the appearance of clinical symptoms of SLE or a positive LE cell reaction.

Pathology.—The significance of hematoxylin bodies found in various mesenchymal organs (heart, lymph nodes, kidney, lung and spleen) in all but four of 45 patients with SLE was emphasized by Klemperer (6). Like the inclusion body in the LE cell the hematoxylin body, which is believed to be specific for this disease, is derived from the nuclear chromatin of cells. The nucleoprotein of the hematoxylin body differs from that of normal nuclei, it is now believed, in the apparent absence of histone, some loss of DNA and the presence of "unusual protein material" (23). As degradation progresses the hematoxylin body appears tinctorially as fibrinoid material.

The lesions in SLE are widespread and involve basically the connective tissues of the body. Vascular structures characteristically affected include the endothelium and walls of capillaries, arterioles and venules which undergo inflammatory and degenerative changes often leading to necrosis (24). The "wire loop" lesions in the glomerular capillaries represent the classical example of such alterations. Pericarditis, verrucous endocarditis and focal myocarditis are common. Periarterial fibrosis in the spleen resembling in appearance an "onion skin" is well known. The epidermis and cutis are

both affected. In the former, hyperkeratosis, atrophy of the rete pegs and liquefaction of the basal cell layer occur. In the cutis, edema, dilated capillaries and cellular infiltrates have been noted. In view of the frequency of joint involvement in this disease, the morphological changes in synovial tissue have received surprisingly little attention. Edema, fibrosis, synoviocytic hyperplasia, deposition of fibrin, and a paucity of inflammatory cells,

TABLE II

INCIDENCE OF CLINICAL MANIFESTATIONS AND LABORATORY CHANGES IN SLE
[Compiled from eight reported series totalling 452 cases (5, 19, 21, 27 to 32)]

	Per Cent
Malaise	100
Fever	93
Arthritis or Arthralgia	88
Positive LE Cell Test	82
Weight Loss	77
Cutaneous Manifestations	62
Cardiac Manifestations	56
Pericarditis	36
Renal Involvement	49
Lymphadenopathy	48
Pleurisy	46
Hepatomegaly	36
Gastrointestinal Symptoms	31
Ocular Lesions	28
Pulmonary Manifestations	25
Positive Serologic Test for Syphilis	23
Psychiatric Abnormality	23
Abnormal Electroencephalogram	22
Splenomegaly	21
Convulsions	19
Hypertension	19
Raynaud's Phenomenon	16
Neuropathy	9

together with vascular changes were reported (25, 26). In the pulmonary parenchyma, bronchi, and pleura, fibrinous deposits and cellular infiltrates occur. Focal and diffuse vascular lesions in the brain and degenerative changes in peripheral nerves have been described. Lymph nodes may undergo marked changes and contain areas of necrosis and hematoxylin bodies.

Clinical manifestations.—The relative frequency of the various signs, symptoms and laboratory changes as reported in eight series totalling 452 cases of SLE are listed in Table II. The LE cell test has been of incalculable help in the recognition of cases of SLE.

Cutaneous lesions of the chronic discoid and acute disseminated types are considered by many authorities to be variants of the same disease, since the transition from one to the other type has been observed by several authors (33). Often many years elapse between the appearance of cutaneous lesions and the development of systemic manifestations. It will be noted in Table II that in 38 per cent of the collected cases no cutaneous manifestations were recorded.

Joint symptoms occur very commonly and often at the onset (30). The degree of involvement may range from mere subjective symptoms of pain to objective changes resembling rheumatic fever (21) and, in 25 to 30 per cent of some series, rheumatoid arthritis (30, 34). Not infrequently cases diagnosed initially as rheumatoid arthritis are recognized, after long periods of observation, to be cases of SLE only by the discovery of LE cells.

Evidence of renal disease was reported in half or more of the cases. The degree of involvement may vary from the presence of only albuminuria or microscopic hematuria to advanced nephritis with uremia. In about one-fourth of the cases, moderate to severe renal disease is present, and the clinical picture may suggest acute or chronic diffuse glomerular nephritis (usually of nephrotic type), pyelonephritis or nephrosclerosis (3). Quite frequently there is a marked disparity between the relatively mild clinical renal manifestations and marked anatomical changes found in the kidneys at necropsy.

In approximately half of the reported cases of SLE, cardiac involvement was clinically detectable and the incidence of heart disease at necropsy attributable to lupus was about 44 per cent (3). Verrucous endocarditis, first described by Libman & Sacks in 1924 (35), and now considered specific for SLE, has been found in about one-third of autopsied cases. It is noteworthy that distinctive and specific cardiac or coronary lesions have been described now in rheumatoid arthritis (36, 37). scleroderma (38), polyarteritis (39), and dermatomyositis (40) as well as in rheumatic fever and SLE.

Raynaud's phenomenon is another "feature-in-common" observed in scleroderma (over 80 per cent) (41), SLE (35 per cent) (30), dermatomyositis (18 per cent) (42), and rheumatoid arthritis.

Treatment and prognosis.—It is the consensus of experienced clinicians that the 11, 17 oxygenated steroids (prednisone, prednisolone, hydrocortisone or cortisone) or corticotropin are therapeutic drugs of choice in all but the mild cases of SLE. These drugs are not curative, however (3, 19, 28, 43, 44, 45). There is a prompt and striking improvement in most of the acute signs and symptoms. Certain changes are irreversible, notably advanced renal, cardiac and cerebral lesions. LE cells may disappear (43, 46), or diminish in number (3, 43) but usually persist (47) during steroid therapy. Prednisone has the advantage of not causing retention of sodium and water or loss of potassium when given in moderate therapeutic doses (44). Some observers recommend continuous treatment (43), others report

that only one-half the patients required uninterrupted therapy (19). Complications of the disease such as cardiac failure, nephropathy or intercurrent infection are treated by conventional measures while steroid therapy is maintained. Thrombocytopenic purpura usually responds quite satisfactorily to splenectomy (48). Relatively prominent among the undesirable effects of steroid therapy are cardiovascular complications, hypertension, convulsions and psychosis. It is important, though often difficult, to distinguish between the complications of the disease process and those of steroid therapy. Other measures being currently evaluated are nitrogen mustard (49, 50), quinacrine hydrochloride, chloroquine (51, 52, 53), and triethylene melamine (50).

The pitfalls encountered in determining average duration of this disease or life expectancy and the effect upon these of steroid therapy were critically considered (3). Using the "life table" method for determining prognosis and measuring duration of disease from time of diagnosis rather than onset, the Johns Hopkins group found that within the first three months after diagnosis, 13 per cent of patients died, but thereafter there was a lower and uniform mortality rate of 10 per cent per year. This group concluded "whether or not life is prolonged by (steroid) therapy cannot at this time be accurately ascertained, but the evidence to date is in the affirmative."

Rheumatoid Arthritis

In this very brief review it will not be possible to mention the numerous important contributions to our knowledge, understanding and better control of this disabling disease. The reader is referred to other recent reviews (1, 2, 54). Significant advances recently made in four areas, prevalence, pathology, serological reactions and treatment, warrant special comment.

Prevalence.—The need for reliable and exact information concerning the prevalence of rheumatoid arthritis (and not merely of "rheumatic complaints" or "arthritis" or "rheumatism") at last has been partially answered (limited to age group 55 to 64) in a community of 48,000 in Lancashire, England (55). Analysis was based on careful histories and physical examinations supplemented by x-rays and serologic (hemagglutination) tests. Employing precise diagnostic criteria the investigators found that the prevalence rates of peripheral rheumatoid arthritis ranged from 1 per cent for men and 3 per cent for women with severe grade, to 11 per cent for men and 27 per cent for women with all grades of rheumatoid arthritis including a past history of this disease.

Pathology.—Few of the lesions found in rheumatoid arthritis have an absolute degree of specificity, yet the composite pattern of pathologic changes is quite characteristic. As in the other connective tissue diseases, abnormal structural alterations may be widely disseminated in rheumatoid arthritis. They may be found in the synovial membrane and articular cartilage of peripheral, sacral, intervertebral and costovertebral joints, in

ligaments, tendons, bursae, subcutaneous tissue (nodules), cardiac structures, blood vessels, skeletal muscles, peripheral nerves, ocular structures, lymph nodes and spleen. Secondary amyloidosis is a common complication occurring in as high as 20 per cent of severe cases at necropsy. Unrelated causally to amyloidosis but occurring not uncommonly in incapacitated patients are chronic intercurrent infections such as bronchiectasis, pneumonitis and pyelitis. A review of these findings has been published recently (54).

Serologic reactions.—The history of this intriguing reaction has been reviewed (54, 56). In the serum of most patients with typical, active peripheral rheumatoid arthritis (and in 95 per cent of those with subcutaneous nodules) is a factor which agglutinates, in higher than normal titers, a variety of substances [hemolytic streptococci, sheep erythrocytes, collodion particles, latex particles (57)] when the latter are coated first with certain protein fractions derived from normal human or sensitized rabbit serum. Recently this factor has been shown to precipitate directly Cohn fraction II of pooled human serum (58). Whether these reactions have the characteristics of an antigen-antibody reaction remains to be determined. The euglobulin fraction of 96 per cent of serums from normal subjects or patients with diseases other than rheumatoid arthritis inhibits the hemagglutination reaction of positive rheumatoid serum, whereas serum euglobulin from 100 per cent of patients with rheumatoid arthritis fails to show this inhibition (59). Certain organic chemical compounds also inhibit this hemagglutination reaction (60). Attempts are currently being made to improve quantitation, and to isolate and chemically characterize the rheumatoid factor. It is hoped that some clue to the etiology or pathogenesis of rheumatoid arthritis may be gained from such studies.

Treatment.—The subject of treatment is complex and the numerous reports on the results of various therapeutic agents are controversial. This is understandable for many reasons. The disease may have unpredictable, spontaneous remissions which vary in frequency and duration from patient to patient. Subjective improvement and change in functional capacity may be influenced by the patient's motivation and other psychologic factors. Precise, objective and reliable measurements of disease activity have been employed in but few of the reported studies. Controls in randomly selected patients have been used infrequently. Composition of the groups of patients has varied widely from one series to another especially in relation to severity and duration of arthritis, presence of irreversible joint changes and duration of follow-up. No completely satisfactory, uniformly effective measure has yet been found which can induce a remission, arrest the progression of destructive changes in the joints, or continue to control symptoms indefinitely without entailing the risk of serious or even fatal toxic effects.

The natural course of rheumatoid arthritis treated by nonspecific, relatively innocuous "conservative" measures has been carefully charted (61, 62). The results may be used as a measure by which the effectiveness of new

agents can be evaluated. There is widespread agreement that initial treatment should be conservative, comprehensive and individualized and should include education and assurance of the patient, relief from internal and external stress, administration of salicylates, physical therapy, corrective exercises, prevention of deformities, and rehabilitation. When such a regimen fails to produce satisfactory results after adequate trial and the arthritis advances relentlessly, one or more of four agents is commonly used: gold compounds (1, 54, 62, 63); corticotropin; 11, 17 oxygenated steroids (prednisone, prednisolone, hydrocortisone or cortisone) (64 to 70); or phenylbutazone (2, 71 to 74). Space will not permit a summary of the reported results and conflicting conclusions (69, 70, 74). Each of these potent drugs has certain advantages and, as mentioned, some serious limitations and hazards.

Progressive Systemic Sclerosis (Systemic Scleroderma)

The number of cases reported in the past decade has increased considerably, and the frequent systemic involvement has been emphasized in most clinical and pathologic reports. Several comprehensive reviews have appeared recently (4, 75, 76, 77).

Pathology.—The morphologic changes in this disease are found principally in the skin, gastrointestinal tract, kidneys, heart, lungs, and joints (78 to 86). The skin shows atrophy of the epidermis and skin appendages, flattening of rete pegs and increased amounts of coarsened hyalinized collagen fibers. Fibrosis of the gastrointestinal structures, lungs and myocardium may occur. Ulceration of esophagus, stomach, duodenum and colon was noted (78). In the kidney, concentric, internal thickening of the medium sized arteries and fibrinoid necrosis of intima and media of the intralobular arteries and arterioles have been described. Synovial biopsies of affected joints reveal focal aggregates of lymphocytes and plasma cells about small blood vessels, villous hypertrophy, loss of synoviocytic lining, generalized fibroblastic proliferation, and deposition of fibrinoid material (86).

Clinical manifestations.—The skin is affected in all cases although it may not always present the initial symptom. Induration, atrophy, ulceration, hyperpigmentation, and vitiligo are common. Raynaud's phenomenon and articular symptoms (often simulating rheumatoid arthritis) are very prominent (41, 87). Calcinosis frequently occurs in subcutaneous tissue, ligaments and skeletal muscle (88). Dysphagia, epigastric fullness and abdominal pain together with radiographic changes in the digestive tract are often present (89 to 95). In some series one-half the cases had pulmonary fibrosis (87, 96) with diminished vital capacity (81). Nonspecific electrocardiographic changes with or without cardiovascular symptoms were reported in 93 per cent of the cases in one series (41). Widening of the peridontal space with partial disappearance of the lamina dura was described (97).

Treatment.—Before the advent of adrenal steroid therapy, a wide variety of drugs had been tried but found ineffective (98, 99, 100). Favorable results

from the use of corticotropin, cortisone and prednisone were reported (96, 99, 101 to 104). Softening of skin, and improvement in joint symptoms and signs, deglutition, respiratory function, appetite and well-being usually follow. However, unsatisfactory results and deaths during (and in one case presumably attributable to) prolonged cortisone therapy also were published (105, 106, 107). Sympathectomy was found useful in properly selected cases with prominent vasomotor symptoms, and facial, esophageal or laryngeal involvement (99). Chelating agents were used with impressive results in a case of scleroderma with calcinosis (108).

Polyarteritis Nodosa[3]

The concept has been advanced that polyarteritis nodosa is not a single clinicopathologic entity but may occur in association with a number of disorders in which necrotizing angiitis develops (113). Thus it was proposed that cases of polyarteritis nodosa be classified according to the following groups: (*a*) classical periarteritis nodosa (Kussmaul-Maier type); (*b*) hypersensitivity angiitis; (*c*) rheumatic arteritis; (*d*) allergic granulomatous angiitis (asthma); (*e*) temporal arteritis, and (*f*) unclassified types.[4]

The role of hypersensitivity in the pathogenesis of experimental and clinical polyarteritis was re-emphasized by many observers (8, 115 to 124). The frequent association of bronchial asthma and this disease was cited (112). Some investigators were impressed with the etiologic relation of diverse microbial agents to polyarteritis (125 to 128). Other workers believed that hypertension was a significant pathogenetic factor (127, 129 to 132). Finally, it was demonstrated that experimental polyarteritis can be produced consistently within a few days following ligation of large branches of the renal arteries in the absence of hypertension, infection or hypersensitivity (133).

Clinical manifestations.—The age at which this disease occurred ranged from one week (134) to 72 years (135). Males predominated in a 3:1 ratio. The relative frequency of organ involvement in 230 cases of polyarteritis studied at the Armed Forces Institute of Pathology was reported (39). Typical lesions were found in the kidneys in 72 per cent, heart 58 per cent, adrenals 51 per cent, pancreas 50 per cent, gastrointestinal tract 47 per cent, liver 42 per cent, spleen 37 per cent, testes 26 per cent, and lungs 23 per cent.

The same authors (39) reviewed the incidence of various clinical manifestations in 607 cases and reported fever in 68 per cent, abnormal urinary constituents in 67 per cent, hypertension 58 per cent, musculoskeletal symptoms

[3] Several good reviews have appeared recently (4, 109 to 112).

[4] The authors of the review believe that rheumatoid arthritis should be added to the above groups since arteritis severe enough to be indistinguishable from polyarteritis nodosa has been encountered repeatedly in cases of rheumatoid arthritis; more frequently in, but certainly not limited to patients who received steroid therapy (114).

50 per cent, abdominal pain 48 per cent, other digestive symptoms 45 per cent, peripheral neuritis 42 per cent, central nervous system symptoms 24 per cent, cough and chest pain 36 per cent and cardiac failure 25 per cent. In other reports skin lesions were found in 20 per cent of the cases (136) and consisted of intra- and subcutaneous nodules, urticaria and purpura. Ocular changes occurred in 10 per cent (137) and consisted of intrinsic or extrinsic muscular disorders, episcleritis, corneal ulceration, iridocyclitis, retinopathy (including cytoid bodies) and optic neuritis (138, 139, 140). Hepatic symptoms, liver abscess and rupture of this organ were described (141, 142).

There are no serologic tests for polyarteritis. Diagnosis is established by locating typical vascular lesions in skin or skeletal muscle biopsies. Since the angiitis is characteristically segmental, the chances of finding a diagnostic lesion in a biopsy will depend, among other things, on the number of tissue sections examined.

Treatment.—The first measure is to determine whether a sensitizing agent may be the cause of the disease and then to eliminate it. Unfortunately, such circumstances are rare. Favorable reports following use of antihistaminics (4), *para*-aminobenzoic acid (143), *para*-aminosalicylic acid (144), and antibiotics (145) remain to be confirmed. On the other hand, many authors have reported adrenal steroids or corticotropin therapy to be beneficial and in isolated cases dramatic (146 to 154). Nevertheless, the response to these hormones has been temporary or unsatisfactory in most cases. The development of polyarteritis in patients with rheumatoid arthritis following cortisone and prednisone therapy has been observed by the authors of this review and by others (114, 155, 156, 157).

Dermatomyositis

During earlier phases of the disease, dermatomyositis may simulate scleroderma, systemic lupus erythematosus or rheumatoid arthritis because symptoms common to the other diseases may occur, such as fever, muscular wasting, mucocutaneous lesions, purpura, photosensitivity, Raynaud's phenomenon, articular symptoms, splenomegaly, lymphadenopathy or leukopenia (4). However, a familiarity with clinical characteristics of the individual connective tissue diseases in conjunction with diagnostic aid offered by muscle and skin biopsy, measurement of daily urinary creatine excretion and negative serologic tests (LE phenomenon and hemagglutination) should enable the clinician to recognize dermatomyositis readily in most cases. Several good reviews have appeared recently (4, 40, 158, 159. 160). It is a serious disease with incomplete spontaneous remissions and usually a fatal outcome within three years (4). Its prevalence is unknown, but it seems to occur less commonly than rheumatoid arthritis or systemic lupus erythematosus, yet it strikes children with greater relative frequency than the other connective tissue diseases here considered.

Characteristic, although nonspecific lesions were described in skin (40, 161), skeletal muscle (40, 42, 161, 162), myocardium (163, 164), gastro-

intestinal tract (160, 164), central nervous system (160), kidneys (165), and in the blood vessels of these structures. The histopathologic changes may be indistinguishable from those found in scleroderma, SLE (166), polymyositis or acute muscular dystrophy (167). Typical lesions occur in skeletal muscle and consist of degeneration of muscle fibrils, focal necrosis, often widespread muscle destruction and inflammation. The latter includes interstitial edema, infiltration of lymphocytes, plasma cells, mononuclear cells, eosinophils and giant cell formation. Arteritis with intimal and medial thickening, fibrinoid deposition, thrombus formation and perivascular infiltration may be present. Biopsy of affected muscle is frequently of diagnostic value.

Clinical and laboratory features.—The most common symptoms consist of weakness, muscular stiffness, tenderness and wasting (symmetrical distribution in shoulder or pelvic girdle), any one of an extraordinary variety of skin eruptions, edema, and fever. In addition, periorbital edema with heliotrope discoloration, joint symptoms, Raynaud's phenomenon and calcinosis may be present (40, 42, 160, 161, 168, 169). Retinal hemorrhages and cytoid bodies were observed (170, 171). The diagnostic importance of abnormal and excessive urinary excretion of creatine with corresponding reduction of creatinine was emphasized (160). The remarkable association of the concomitant occurrence of neoplasms (no organ specificity) and dermatomyositis [18 per cent in one series (172)] was observed repeatedly.

Treatment.—As in scleroderma so in dermatomyositis, the many different drugs employed before the introduction of cortisone have been found of little value (40, 173, 174). Although corticotropin or the 11, 17 oxygenated steroids are not uniformly effective and not without risk, they should be given a trial for several months in all cases (except when absolute contra-indications exist), and if helpful they should be continued indefinitely (4, 175, 176). Intercurrent infections should be looked for constantly and when detected should be treated promptly and adequately.

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ACTIONS OF HEPARIN OTHER THAN THOSE ON COAGULATION[1,2,3]

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Heparin was discovered 40 years ago (1, 2) via its anticoagulant properties. Many other activities of heparin have now been found; as yet its ordinary physiological effects are not defined. In this review we shall indicate some of the wide variety of activities which have been observed for heparin in biological systems. Some of these may be its ordinary effects; some are potentially useful therapeutic actions.

The Relationship to Lipide Metabolism

The heparin-activated lipemia clearing system.—Hahn (3) observed rapid clearing of the lipemic turbidity of postprandial dog plasma following intravenous heparin injection. This was confirmed and extended (4, 5) and as the subject has been quite recently reviewed (6, 7, 8) we shall indicate only the salient points. Injection of heparin into animals or men with postprandial lipemia leads to clearing of turbidity and disappearance of chylomicrons. Plasma removed minutes to hours after an injection of heparin will cause clearing *in vitro* of lipemic serum, washed chylomicrons or fat emulsions. The reaction is enzymatic and free fatty acids are released from triglycerides; it is inhibited by protamine and other basic substances. Enzyme is released from peripheral tissues and is apparently destroyed in the liver. Similar activity is elicited by a fatty meal or perfusion of plasma containing chylomicrons through peripheral parts of an animal. Hence it appears that this is a normal mechanism. There is some question as to whether it is normally activated by heparin. Recent presumptive evidence in favor of this has been presented (9). That heparin is not the activator or not the only activator of the clearing system was suggested by observations that substances other than heparin, some not sulfated, e.g. glycogen, activated the system (10).

Heparin and the Pathogenesis of Atherosclerosis

The clearing response in relation to increasing age and manifest arteriosclerosis.—Older subjects and persons with manifest arteriosclerosis have prolonged high levels of lipemia following a fatty meal (11, 12, 13). In arteriosclerotics clearing of postprandial lipemia after heparin injection was

[1] The survey of literature pertaining to this review was completed in September, 1956.

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[3] Original work cited was supported in part by a grant-in-aid from the United States Public Health Service (#H-2141).

found to be less than in controls (14, 15), suggesting diminution of available enzyme. Recent analysis under better standardized conditions indicates no decrease in heparin-activated clearing factor with age or manifest coronary arteriosclerosis (16). If this is so then there is the possibility that the available heparin, or other activator of clearing factor, is diminished. Evidence for a decreased heparin concentration in the blood of persons with arteriosclerosis (17, 18, 19) is tenuous. Delay in clearing may be attributable to other factors, e.g., pancreatic lipase deficiency (16).

Effects of heparin on blood lipides in atherosclerosis and related conditions.—Aberrations in blood lipide concentration and distribution have been observed in arteriosclerosis and in diseases predisposing to arteriosclerosis (20 to 28). Redistribution of the lipoproteins among the various density classes occurs after a single intravenous dose of heparin (25, 29 to 32). Some changes persist for from 24 to 72 hours (31). An increase in the mobility of the electrophoretically defined lipoproteins occurs (33 to 38), possibly because of uptake of the free fatty acids by the lipoproteins (38). Changes in extractable blood lipides of normal, atherosclerotic, nephrotic and hyperlipemic persons following a single heparin injection have been observed: neutral lipides decreased, without consistent changes in cholesterol or phospholipide fractions (33, 39, 40). After prolonged intermittent therapy no significant persistent alterations were observed (40, 41).

Heparin therapy in atherosclerosis.—If alterations in blood lipide pattern are a significant part of the pathogenesis of atherosclerosis then prolonged heparin therapy might be, exclusive of its role as anticoagulant, effective in slowing progression of the disease. Evidence has been presented that this is so (40). During the one and a half year period of observation there were 4 cardiovascular deaths in 105 heparin-treated patients and 21 deaths in 117 placebo-treated patients. Statistically this is a significant difference. There were 5 non-fatal recurrent infarcts in the heparin-treated and 18 in the control group. The treatment if efficacious has the advantage over anticoagulant therapy in so far as the possibility of hemorrhage is reduced. It is to be hoped that further evidence will soon be produced.

Prevention by heparin of atherosclerosis induced by cholesterol feeding in rabbits was reported (29, 42, 43); others reported partial protection (44, 45), and one group reported no protection (46). The weight of evidence is in favor of protection. Associated with heparin administration cholesterol levels were observed to be lowered (42, 46, 47), not lower (44), or elevated (45), and serum lipoprotein shifts attributable to heparin were seen (47). In cholesterol-fed chicks, heparin was found to lower serum cholesterol values (48, 49) and to reduce severity of atherosclerosis in one investigation (48) and not in another (49).

The relationship of mast cells to clearing factor activation and atherosclerosis.—Heparin is in mast cells (50, 51), stimulation of which in peptone or anaphylactic shock was associated with activation of the clearing system in the dog (52) but not in rats (53) or other animals (50). This again raises

the question of the ordinary participation of endogenous heparin in the clearing system. Evidence has been produced indicating an inverse relationship between the number of mast cells in the peripheral tissues of animals (54) and humans (55) and the susceptibility to atherosclerosis.

Psoriasis and the nephrotic syndrome.—Evidence that lipide metabolism was altered in psoriasis led to examination following a fat meal of the chylomicrons (56), the serum lipoprotein density classes (57), and the α and β lipoproteins (58) with evidence of alterations which are reversed by heparin. A saline placebo was as effective as heparin in clinical therapy (59). Heparin therapy produced alterations in serum lipoproteins of patients with the nephrotic syndrome (33, 39) but had no effect on the clinical manifestations. A favorable effect was reported in three cases of diabetic glomerulosclerosis (60).

Blood Flow and Blood Pressure

Peripheral flow.—Increased blood flow in perfused organs has been reported with heparin (61, 62), but no significant increase in exercise tolerance of patients with peripheral vascular disease and intermittent claudication was observed with prolonged intermittent heparin therapy (63, 64, 65). Neither cerebral blood flow nor oxygen consumption following a single dose of heparin was increased (66, 67) whereas significant increases in forearm oxygen consumption were reported (68).

Angina pectoris.—Following the initial report of a beneficial effect of heparin in angina pectoris (69) many confirming reports appeared (29, 70 to 74). More carefully controlled studies showed that placebos have a pronounced effect to which intermittent therapy with heparin adds little (75 to 78). The question was re-opened by the report (79, 80) that anginal attacks with associated electrocardiographic and ballistocardiographic changes could be regularly produced following a fat meal in patients subject to angina. Attacks coincided with the peak of the lipemia and could almost invariably be relieved in a few minutes by a small dose of heparin intravenously. Attacks not relieved by placebo responded to heparin.

Hypertension.—Evidence for an ameliorating effect of heparin on hypertension in humans (81, 82) has been produced. A better controlled study did not bear this out (83), but in experimentally induced hypertension in rats a significant effect was recorded (84).

Inflammation and Related Processes

Enzymes.—Inhibition of proteolytic enzymes by heparin (85), and activation of plasma fibrinolysin (86) were observed. Adenylic deaminase was inhibited but not several other enzymes including hexokinase (87); *in vivo* heparin altered mouse liver ribonuclease activity (88). *In vitro* heparin (and related compounds) was a competitive inhibitor of hyaluronidase (89).

Serum complement and antibody.—*In vitro* heparin has been found to inactivate serum complement (90, 91); *in vivo* a situation now known to damage

mast cells and liberate heparin was associated with decreased complement activity (92) although injection of heparin did not lower complement levels (90). Hemolytic antibody may be inactivated by heparin (93).

Blood cells.—Heparin *in vitro* increased the phagocytic index of rat (94) and human (95) leukocytes; *in vivo* it produced a transitory capillary thrombocytopenia (96).

Heparin, histamine, and serotonin.—These three important substances have now been found in mast cells (50, 51, 97), from which they are apparently released in a variety of injuries (98). The unlikely suggestion that the action of heparin is to protect against histamine has been made (99). The three substances are probably secreted by the mast cell and operate interdependently in the response to injury.

Tissue growth and wound healing.—Reversible inhibition of cell proliferation in tissue culture was found (100, 101). It was suggested that heparin interfered with mitosis (102) and nucleic acid metabolism (103). Reticular fibers are formed in the presence of mast cells or heparin (104). Precipitation of "collagen" fibers from precursors by heparin (105) is said not to be specific (106). Heparin tolerance was found increased in persons with keloids (107). Heparin applied topically slowed wound healing (108) and perhaps altered keloid formation (109).

Experimental inflammations.—Heparin prevented the manifestations of anaphylaxis (110, 111) including the Arthus reaction (112) and uveitis (113). It was found to reduce the intensity of serum nephritis in dogs (111). In nephrotoxic nephritis heparin reduced the changes observed by some (114, 115) and augmented those observed by others (116). The tissue necrosis in the Shwartzman reaction was abolished (118, 119) as were the renal changes induced by cortisone in the rabbit (117).

Inflammatory disease.—The influence of heparin on components of inflammation have induced trials in rheumatic fever (120, 121, 122). A positive effect was reported on the exudative manifestations (112). Heparin tolerance in rheumatic fever (123, 124) and lupus erythematosus (125) was found increased. The participation of heparin in fibrinoid formation was suggested (126, 127). Ameliorating effects in infections were reported (128, 129).

Endocrine Interactions

In vitro ACTH neutralized anticoagulant effects of heparin (130), and heparinized plasma inactivated ACTH (131) and melanophore stimulating hormone (132). *In vivo* heparin was said to reduce blood sugar elevation induced by ACTH (133). The rise in fasting blood sugar induced by heparin was mimicked by epinephrine and blocked by an adrenergic blocking agent (134). Heparin did not antagonize ACTH-induced ascorbic acid depletion of the adrenal (135) or eosinopenia (133, 136). By itself it induced and with ACTH augmented thymus shrinkage in rats (137, 138). Evidence of action on nerves, neurochemical mediators, or both, was presented (139, 140).

Comment

The foregoing enumeration of many reported actions of heparin is interesting if somewhat confusing. The same confusion exists with heparin as with many substances once laboratory curiosities and now recently available for widespread use. Trials in therapeutic situations are colored by psychological interactions; trials by injection elicit a multiplicity of effects in patterns which, while bearing some relationship to physiological function, are distorted by the mode of administration and the observational scheme used. Trials *in vitro* have minimal presumptive meaning. The work done thus far has begun merely to open our eyes to possible effects of heparin. Its ordinary physiological function as well as its therapeutic effects will be found in relation to its chemical constitution and its site in the body.

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SPECIAL THERAPEUTICS (HELMINTHIC DISEASES)[1]

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The exposure of large numbers of military personnel to infection by various protozoan and helminthic parasites during World War II and the Korean conflict greatly stimulated research on the therapy of these infections. Agents are now available for the treatment of various helminthic diseases for which no treatment existed a few years ago, and new, safer and more effective remedies have been found for many others. Emphasis here will be placed on helminthic diseases prevalent in this country, and those acquired by service men during the war, or likely to be contracted in overseas travel.

Intestinal Helminths

Roundworms.—The intestinal roundworms are by far the commonest helminthic parasites in this country, and of these the pinworm, *Enterobius vermicularis*, receives the most attention. Whether or not it is responsible for the multiplicity of symptoms ascribed to it is debatable, but the development of a "pinworm neurosis" on the part of the parents of infected children often demands therapy even when the child's symptoms may not. Treatment, to be successful, must take into consideration the extraordinary ease with which this parasite, once established in a family, is transmitted from one member to another. Adult "reservoirs" of infection are common, and frequently asymptomatic; Schüffner & Swellengrebel (1) have pointed out that while the oral route is the most important means of re-infection in children, adults can maintain a chronic infection by means of ova which hatch in the perianal area and crawl actively back into the rectum where they grow to maturity. This process is known as "retrofection." It is advisable to examine all members of a family when one is found to be infected, so that all infected persons may be treated at the same time. An excellent discussion of the general management of enterobiasis is given by Kean (2).

While a treatment of short duration offers obvious advantages, it is highly desirable to prolong it sufficiently so that the general environmental sanitary measures which are of such great importance may be carried out completely. Gentian violet has been used for some years in the treatment of pinworm infection, and until recently was the most effective drug in use [Wright & Brady (3)]. However, even in its enteric-coated form, it may cause severe gastrointestinal upsets. Piperazine compounds were first introduced for the treatment of *Enterobius* infections by Mouriquand *et al.* (4), and have achieved considerable popularity. Many reports, especially those of White

[1] The survey of literature pertaining to this review was completed in July, 1956.

& Standen (5), Rachelson & Ferguson (6), and Brown & Chan (7), indicate that a single course of treatment will cure 80 to 100 per cent of cases. Negligible toxic effects are described, but Combes *et al.* (8) caution against the use of the drug in patients with impaired renal function. The best results are obtained with doses equivalent to approximately 50 mg. of piperazine hexahydrate per kg. of body weight daily for 10 to 14 days [Brown & Chan (7)]. The same dosage, administered in two seven-day courses, with a seven-day rest period between, is not as efficient [Ricci & Corby (90)], and the more intensive treatment is just as well tolerated.

Oxytetracycline (Terramycin) has been used with considerable success against *Enterobius* [Wells *et al.* (10)]. Owings (11) gave 0.5 gm. daily in divided doses for four days to children under five years of age, double that dosage to older children, and cured 85 per cent of cases. He did not consider the drug suitable for routine use. Piperazine was found superior to oxytetracycline by Bumbalo *et al.* (12), and White & Standen (5) preferred it to gentian violet and to *p*-benzylphenylcarbamate (Diphenan). Dawsett & Brown (13) also considered Diphenan to be relatively ineffective. Another drug which has enjoyed some popularity is phenothiazine, a highly toxic compound which may cause a hemolytic anemia [Kuitunen-Ekbaum (14); Keizer (15)].

A number of compounds have been introduced in recent years for the treatment of the large intestinal roundworm, *Ascaris lumbricoides*. Among these are diethylcarbamazine (Hetrazan), used by Oliver-Gonzalez *et al.* (16), Etteldorf & Crawford (17), and Loughlin *et al.* (18) with good success, and various papain derivatives as described by Jonxis & Bekius (19) and Stransky & Reyes (20). Hoekenga (21, 22) compared a number of remedies, including diethylcarbamazine, papain, and hexylresorcinol. He considered that none of them gave outstanding results, but did find piperazine to be very effective. Unlike other ascaricides, piperazine does not require pre-treatment fasting, or pre- or post-treatment purgation. Brown (23) recommended the following dosage schedule, based on patient weight:

30 to 50 lbs.	—2.0 gm. piperazine hexahydrate
51 to 100 lbs.	—3.0 gm. piperazine hexahydrate
over 100 lbs.	—3.5 gm. piperazine hexahydrate

Using these amounts, he secured a 74 per cent cure rate with one day of treatment, and 94 per cent with two days. Swartzwelder, Miller & Sappenfield (24) eliminated nearly 100 per cent of infections with a single-dose treatment at 70 mg. per pound of body weight, giving a maximum of three gm. of the drug. They observed that the worms were paralyzed, and evacuated slowly over a one to four day period.

Hookworm disease, in contrast to asymptomatic hookworm infection, is uncommon in this country at present. It is always questionable whether treatment is justified in a patient exhibiting no symptoms, especially if circumstances are such that he is unlikely to serve as a source of infection for

others. In severe hookworm disease, it is generally advisable to treat the anemia before attempting anthelmintic treatment. The administration of iron in such cases is discussed by McFadzean & Wong (25). Piperazine is almost entirely ineffective in the treatment of hookworm infection [Hoekenga (22)]. Diethylcarbamazine is effective if administered in fairly high doses over a prolonged period (10 mg. per kg. of body weight daily for 15 days), but Ghanem (26) considered both tetrachlorethylene and hexylresorcinol approximately as effective; they may be given in single doses. Carr, Picardo Sardá & Nuñez (27) considered tetrachlorethylene the drug of choice. They treated very large numbers of persons with this drug and consider it safe and effective, if given without pre- or post-treatment purgation. The former did not increase its efficiency, the latter was definitively contraindicated. They gave 0.05 to 0.06 ml. of tetrachlorethylene per pound of body weight, with a maximum dose of 5 ml. Jelliffe (28) warns against the use of this drug in patients with ascariasis, because it is likely to provoke the latter worms into disastrous migratory efforts.

Tetrachlorethylene is contraindicated in hepatic disease [Goldbloom & Boyd (29)]; hexylresorcinol or diethylcarbamazine should be used instead. Hexylresorcinol is administered in the form of hard gelatine capsules containing 0.1 or 0.2 gm. of the drug. The adult dose is one gm.; for children give 0.1 gm. per year of apparent age up to six years. Older children receive the adult dose. The drug must be given to very young children with caution, as the capsules will cause severe burns of the buccal mucosa if crushed.

Whipworms (*Trichuris trichiura*) in small numbers probably give rise to no symptoms, and in view of the difficulty with which this parasite is eradicated might best be ignored. Larger numbers of worms may produce a severe dysentery, and Jung & Beaver (30) emphasized the serious complications which may occur in children. Peroral medication is rather ineffective. Hoekenga (22) found that administration of 2 gm. of piperazine citrate daily for seven days eliminated about one-third of infections. Jung & Jelliffe (31) considered hexylresorcinol enemas to be the treatment of choice. They advised a preliminary cleansing enema, followed by slow instillation of 500 to 700 ml. of 0.2 per cent hexylresorcinol in water or glycerine solution. This enema should be retained for one-half to one hr.; the perineum, buttocks and thighs must be covered with a protective coating of petroleum jelly to prevent burning of the skin. Basnuevo (32) suggested for children the administration of 15 to 20 ml. of a 0.33 per cent hexylresorcinol solution per pound of body weight.

Infection with *Strongyloides stercoralis* is not usually regarded with the seriousness which this condition warrants. While small numbers of worms may produce no symptoms, the parasite is probably capable of unlimited reproduction within the body of the host, and for this reason even asymptomatic cases should be treated. Kyle, McKay & Sparling (33) have given an excellent general account of the disease, with a detailed report on a fatal case. They recommended the use of gentian violet, one grain three times

daily for a total of fifty grains, by mouth, or if this is unsuccessful its intraduodenal or intravenous administration.

Diethylcarbamazine has been used in the treatment of strongyloidiasis by several workers. Chernin (34) found that doses of six mg. per kg. of body weight three times daily for six days cured only two out of seven patients, and that this high dosage caused toxic symptoms in five of them. Piperazine citrate has received limited trial, but was found to be ineffective in what appears to be adequate dosage [Swartzwelder, Miller & Sappenfield (35)].

Tapeworms.—The observation by Culbertson (36) that quinacrine (Atabrine) is active against *Hymenolepis nana* in mice has led to the virtual abandonment of the classical, drastic taeniafuges. Berberian (37) published the first report of the treatment of human *H. nana* infections with Acranil, a synthetic drug related to quinacrine. Since that time, quinacrine has been used in the treatment of taeniasis (both *Taenia saginata* and *Taenia solium*) and *Diphyllobothrium latum* infections, in addition to hymenolepiasis. Sodeman & Jung (38) recommended the administration of 0.8 gm. of quinacrine hydrochloride for taeniasis in adults. A milk diet is given on the day preceding treatment, and the patient receives a purge in the afternoon. A saline enema the next morning is followed by 0.2 gm. of quinacrine every five min. for a total of four doses. Sodium bicarbonate may be administered with the quinacrine to prevent nausea. Two to four hours after the last dose of quinacrine, the patient is again purged. Post-treatment purgation is most essential as the worms are apparently paralyzed by the drug, but not killed. Halawani *et al.* (39) emphasized the importance of proper preparation of the patient. Hornbostel & Dörken (40) recommended a "strategic treatment" in taeniasis; they located the worm radiographically and passed a tube into the proximal jejunum in an attempt to "aim" the quinacrine as a dilute solution at the scolex of the tapeworm. Administration of quinacrine by duodenal sound was also recommended by Faiguenbaum & Donckaster (41) in *Diphyllobothrium* infection, and by Seaton (42) for taeniasis. The latter recommended giving one gm. of quinacrine dissolved in 100 ml. of warm water, leaving the tube in place for administration 15 or 20 minutes later of one and a half or two oz. of magnesium sulfate in warm water. Nor El Din (43), in addition to a preliminary intensive treatment with quinacrine, continued the drug at the rate of 0.1 gm. three times daily for seven days. This practice would probably be of value in cases apparently resistant to treatment.

While quinacrine is a very safe drug, it is irritating to the gastric mucosa, and nausea and vomiting may follow its administration in the doses necessary to treat tapeworm infection. This can be extremely dangerous in *T. solium* infection, where gravid proglottids of the worm entering the stomach may begin their larval development, giving rise to cysticercosis (see below). Despite the prophylactic use of phenobarbital and sodium bicarbonate, Hoekenga (44) found that about 20 per cent of patients became nauseated upon taking quinacrine by mouth. It is probably safest to treat *T. solium*

infections by intraduodenal instillation of the drug, after thorough sedation of the patients.

Chloroquine and amodiaquine have both been found to possess taeniafugal properties similar to quinacrine [Basnuevo & Blanco Rabassa (45); van Grunderbeeck & Penson (46)], but they do not appear clearly superior to the latter drug.

Flukes.—None of the intestinal trematodes is of sufficient importance in American practice to consider here. In general it may be said that while numerous drugs have been advocated for the treatment of these parasites, hexylresorcinol seems to be as effective as any, and should be given in the same dosage as recommended for the treatment of hookworm disease.

Extra-Intestinal Parasites

Filarial worms.—Six species of filariae are parasites of man. Only three of these are of sufficient real or potential interest to physicians practicing in the United States to consider here. The filariae are all long-lived, and may persist for years after their host leaves the area in which they were acquired.

Bancroftian filariasis, caused by *Wuchereria bancrofti* and transmitted by mosquitoes, came into prominence in American medical thought as a result of World War II, when several thousands of our troops in the Pacific Theatre contracted primary filariasis. This caused great concern, although it was soon appreciated that the primary disease does not inevitably lead, in the absence of re-infection, to elephantiasis.

During the past decade a number of new drugs have been found which are active against the adult worms in the lymphatics, the microfilariae in the blood stream, or both. Santiago-Stevenson *et al.* (47) and Hewitt *et al.* (48) reported on the use of diethylcarbamazine for control of filariasis in Puerto Rico and the Virgin Islands, as the outcome of several years study of the actions of the drug in experimental filariasis in the cotton rat [Hewitt *et al.* (49 to 52)]. Subsequent reports by Galliard & Mille (53), Beye *et al.* (54), Kessel *et al.* (55) and others confirm the effectiveness of diethylcarbamazine as a microfilaricide, and indicate that it may also kill the adult worms or prevent their producing more microfilariae. The original dosage recommended was two mg. per kg. of body weight, three times daily, for from one to three weeks. Many different dosage schedules have been tried since, but Kessel and his co-workers in French Oceania now recommend three to six mg. per kg. of body weight once a month for periods of 12 months or longer, in mass treatment campaigns. In the treatment of individual patients, a preliminary intensive treatment may be combined with the once-a-month dosage over an extended period. The final result of repeated small treatments over an extended period of time seems better than that of intensive treatment confined to a short period. While diethylcarbamazine is essentially non-toxic, patients under treatment may develop sensitivity reactions to antigenic substances liberated on death of the microfilariae or adult worms. These must be treated symptomatically.

Culbertson (56) compared the action of various arsenical and antimonial drugs in filariasis and concluded that while several exhibited some activity, only ethylstibamine (Neostibosan) gave real promise. Otto *et al.* (57) found that arsenamide, administered intravenously in daily doses of 1.0 mg. per kg. of body weight for 12 to 15 days sharply reduced the number of microfilariae in the circulating blood. Patients became microfilaria-free slowly, over a period of several weeks or months, but remained so longer than after similar courses of diethylcarbamazine. The antimonial and arsenical drugs have not been introduced into general use in treatment of filariasis, because of their toxicity, expense, and the necessity of intravenous administration. Suramin (Bayer 205, Naphuride), which is a synthetic organic preparation containing no metal, has been used by Burch (58) but seems less effective than the other drugs mentioned. Hawking (59) has recently reviewed the chemotherapy of this and other filarial dieases.

Diethylcarbamazine treatment sharply reduces the incidence of filarial lymphangitis, and there is some evidence that early elephantoid changes may be to some extent reversible with proper medication. Late elephantiasis cannot be affected by filaricidal or microfilaricidal drugs, and requires surgical intervention or supportive treatment, a subject reviewed by Knott (60). Thooris (61) described an improved bandaging method, incorporating Unna's paste. Markell & Kerrest (62) found the administration of cortisone of benefit in advanced elephantiasis. They gave 25 mg. of cortisone acetate four times daily for initial periods of 30 days, with marked improvement which usually peristed several months after therapy was discontinued.

Onchocerciasis, infection with the filaria *Onchocerca volvulus*, which is transmitted by black flies (*Simulium*) is widespread in Africa and also occurs in Mexico, Guatemala and Venezuela. The worms live in subcutaneous nodules, from which they liberate microfilariae into the skin and subcutaneous tissues. The microfilariae may penetrate into the orbit, and produce blindness.

Mazzotti & Hewitt (63) treated onchocerciasis with diethylcarbamazine, giving two mg. per kg. of body weight three times daily for 15 to 21 days. They found that the microfilariae in the skin disappeared quickly; Mazzotti (64) considered that this treatment had a decided beneficial effect on the ocular symptoms. Microfilariae slowly reappear in the skin after treatment, an indication that adult worms are still alive. Martinez Báez (65) found that 60 per cent of worms removed by biopsy two months or more after treatment were "altered" (injured or killed), and that this figure rose to 75 per cent a year after treatment. Burch (58, 66) and Burch & Ashburn (67) report on the use of suramin and diethylcarbamazine. They found that intravenous suramin in doses of 0.5 gm. initially, followed by five to seven weekly injections of 1.0 gm., produces a more permanent cure than diethylcarbamazine, although its action on microfilariae is slower.

Diethylcarbamazine treatment produces allergic skin reactions in onchocerciasis patients with such regularity that Mazzotti (64) suggested

administration of the drug as a diagnostic test. These reactions may be acutely painful; Markell (unpublished data) has found that they may be suppressed by administration of cortisone.

Wanson (68) suggested that diethylcarbamazine may be used prophylactically by persons in endemic areas, to prevent maturation of the larval forms.

Loa loa, the "eye worm" of man, occurs in Africa where it is transmitted by flies of the genus *Chrysops*. The adult worms inhabit the subcutaneous tissues, where they migrate freely. Rarely, and dramatically, they may invade the conjunctiva, where they are readily removed surgically. The parasite produces no serious damage, but its presence is marked by occasional pruritis and temporary allergic inflammatory reactions, known as Calabar swellings.

Diethylcarbamazine has been used with good results in loiasis [Shookhoff & Dwork (69); Murgatroyd & Woodruff (70); Schneider (71); Stones (72)]. Dosages recommended are in the neighborhood of 100 mg. three times daily for seven to ten days. The treatment may be marked by temporary exacerbation of the allergic symptoms, and repeated courses may be required to kill the adult worms.

Lung flukes.—Paragonimus westermani is found in some of the Pacific islands and parts of Asia, Africa and northern South America and has been contracted by military personnel stationed in these areas. While it commonly occurs in the lungs, it may develop in other tissues. Cerebral involvement is not uncommon. Kay (73) reported a case, diagnosed in Virginia, in which the parasite localized in the anterior abdominal wall. Emetine hydrochloride has been the standard treatment for paragonimiasis for some years, but is not highly effective. Tillman & Phillips (74) report symptomatic improvement and some apparent cures following its use. Komiya *et al.* (75) tried a combination of emetine and various sulfonamides, but their results were poor. Roque, Ludwick & Bell (76) used both emetine and stibophen (Fuadin) in the treatment of cases contracted in Korea, and found both to be moderately effective.

The most encouraging results to date have come from the use of chloroquine. Chung & Hou (77) and Chung, Ch'en & Hou (78) have reported on its use in a number of patients, some of whom had received only temporary symptomatic relief from emetine. They have given doses up to 0.25 gm. of chloroquine base twice daily in young children, and double that dose in adults, continued over periods up to 231 days. The drug is well tolerated, and apparently kills the adult worms if treatment is long enough continued. While not mentioned in these reports, occasional cases of chloroquine intolerance may be encountered; if gastro-intestinal disturbances are severe, a few days interruption of therapy may eliminate them.

Liver flukes.—No indigenous infections have been reported from this country, although fascioliasis might be expected to occur sporadically, as *Fasciola hepatica* is common in sheep and cattle. In Cuba and elsewhere

F. hepatica has been reported as a human parasite [Arenas *et al.* (79)], and the related *Fasciola gigantica* infects man in Hawaii [Alicata (80); Stemmermann (81)].

Chloroquine has been used in treatment of infection with the Chinese liver fluke, *Clonorchis sinensis*, a parasite found in this country mainly in immigrants from China and occasionally in other people who have resided in endemic areas. Basnuevo (82, 83) found that 0.5 gm. of chloroquine daily for 20 days apparently cured about two-fifths of cases. Crane, Bush & Won (84) report similar results on giving 0.5 gm. three times daily for three weeks, but Chung, Weng & Hou (85) claim considerably better success for similar dosages, when administered over periods of 20 to 53 days. Sadun, Chamnarnkit & Chetanasen (86) treated infections caused by the closely related fluke *Opisthorchis viverrini*, with chloroquine and with quinacrine. Quinacrine was apparently inactive, but chloroquine gave encouraging results. It is apparent that while chloroquine is not wholly satisfactory for the treatment of clonorchiasis, it is superior to any of the drugs previously used. It seems possible that cure rates would be higher in this disease if the drug were administered over periods comparable to those used in treatment of paragonimiasis.

Blood flukes.—Schistosomiasis is fortunately rare in this country, although Puerto Ricans sometimes bring *Schistosoma mansoni* with them when they come to the mainland. The Oriental blood fluke, *Schistosoma japonicum*, is occasionally seen in immigrants from Asiatic countries, and infections with this parasite were contracted by some hundreds of our forces in the Pacific area. The third species, *Schistosoma haematobium*, which causes vesical (urinary) schistosomiasis, is seen here only occasionally in persons coming from endemic areas.

An enormous amount of work has been done in the past few years in the development and evaluation of new drugs for the treatment of these diseases. The antimonial compounds long used in schistosomiasis (tartar emetic and stibophen) have been employed by Alves & Blair (87) and others in intensive one or two day courses of treatment. Miracil D (1-diethylaminoethylamino-4-methylthioxanthone; Nilodin) was synthesized during World War II in Germany, and has received extensive field trials [Blair, Hawking & Ross (88); Blair *et al.* (89); Alves (90)]. It possesses the advantage that it may be administered by mouth, but is a decidedly toxic drug. Most (91) reviewed the therapy of these diseases, and concluded that tartar emetic is the drug of choice for treatment of all three parasites, although the dosage required varied with the species. For further details of therapy see Most *et al.* (92). Two excellent general review papers are those of Fairley (93) and Meleney (94).

Larval Parasites

Under this heading the treatment of cysticercosis, hydatid disease, larva migrans (cutaneous and visceral) and trichinosis will be considered briefly.

Cysticerosis is infection with the larval form of *Taenia solium*, and is

caused by ingestion of the eggs of this parasite. Cysticerci may develop in virtually any organ or tissue of the body, and symptoms will depend upon their localization. Dixon & Hargreaves (95) gave an excellent clinical discussion of the disease, for which they were able to suggest only surgical treatment. More recently Mazzotti & Treviño (96) have used diethylcarbamazine on patients with subcutaneous cysticercosis. Administration of diethylcarbamazine in low dosage resulted in the disappearance of all cysticerci in two of the three patients treated, and of some of those in the third. This treatment would have to be undertaken with caution, as cysticerci may produce no symptoms at all until they die and begin to disintegrate.

No new treatments have been suggested for hydatid disease, or echinococcosis, and present opinion strongly favors early surgical removal. Barrett & Thomas (97) gave an excellent review of the pathology and treatment of pulmonary hydatid disease, and favored surgical removal, while Miller (98) demonstrated that pulmonary hydatids frequently rupture into a bronchus and resolve spontaneously, and suggested a cautious expectant treatment.

Cutaneous larva migrans, or creeping eruption, is a dermatitis caused by abortive attempts of hookworm larvae of species parasitic in lower animals to parasitize man. They are able to penetrate the skin, but not to complete their migration from there to the intestinal tract. Horton (99) found diethylcarbamazine useful in treatment of this condition. He gave two mg. per kg. of body weight for periods up to 21 days. Visceral larva migrans, a syndrome recently described by Beaver *et al.* (100) is caused by ingestion of ova of dog or cat ascarids. These ova produce larvae which because of their inability to complete the migratory cycle in an abnormal host remain in the lungs or liver. Pulmonary migration of these larvae may cause severe and long-continued respiratory embarrassment. Heiner & Kevy (101) suggest symptomatic treatment with corticosteroids or ACTH. Dent *et al.* (102) used cortisone in one case with apparent benefit.

The first therapeutic agents of any real value in the treatment of trichinosis have been provided by the introduction of ACTH (adrenocorticotropin) and the adrenal steroids. Davis & Most (103) and Luongo, Reid & Weiss (104) used ACTH with dramatic results, and Rosen (105) and others have been equally impressed with the action of cortisone in severe trichinosis. Stoner & Godwin (106), Coker (107) and others have shown that the intestinal phase of the disease persists longer in cortisone-treated animals, and that as a consequence more larvae are produced. This suggests that cortisone treatment may be a double-edged sword. Oliver-Gonzalez & Hewitt (108) demonstrated that diethylcarbamazine destroyed adult *Trichinella* in experimental animals, and Chan & Brown (109) found that piperazine had the same effect. The adult worms may live as long as 54 days in the human intestine [Stryker (110)], and probably longer if cortisone is administered. In cases where steroid therapy is indicated, it is probably best to attempt eradication of the adult worms in the intestine at the same time, with the use of large doses of piperazine or diethylcarbamazine.

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TOLERANCE TO AND PHYSICAL DEPENDENCE ON OPIATES, BARBITURATES, AND ALCOHOL[1]

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The terms "tolerance" and "physical dependence" must be defined and their relationship to the overall problem of addiction illustrated. In addition, it is necessary to outline the limitations as well as the general purpose of the review. "Tolerance" means a decreasing effect on repetition of the same dose of a drug; "physical dependence" refers to the development of an altered physiologic state which requires continued administration of a drug to prevent the appearance of a characteristic illness, called an "abstinence syndrome." The level of dosage required for the development of physical dependence varies considerably with different drugs. For example, continuous administration of therapeutic doses of morphine for 28 days will create a moderate but definite degree of dependence, whereas administration of therapeutic doses of barbiturates for 90 days does not. The continuous administration of a drug in such a schedule of doses that some kind of drug effect is constantly present is referred to in this review as "chronic intoxication."

Since production of physical dependence by a drug is considered primafacie evidence that it is addicting, a definition of addiction is in order. It is a

> state of periodic or chronic intoxication detrimental to the individual and to society, produced by the repeated consumption of a drug (natural or synthetic). Its characteristics include: (*a*) an overpowering desire or need (compulsion) to continue taking the drug and to obtain it by any means, (*b*) a tendency to increase the dose, and (*c*) a psychic (psychological) and sometimes a physical dependence on the effects of the drug.

This is the definition of the Committee of Experts on Drugs Liable to Produce Addiction of the World Health Organization. It is noted that this definition includes drugs which do not produce physical dependence; for example, marihuana, cocaine, and certain sympathomimetic amines (amphetamine and methamphetamine). Although these are dangerous drugs when abused, paucity of space precludes consideration of them. For the same reason, the extremely important problem of psychic dependence will not be discussed. Theories of tolerance and physical dependence will not be covered since there are recent comprehensive reviews of these subjects [Isbell & Fraser (1); Seevers & Woods (2); Eddy (3); and Seevers (4)]. References to the literature will cover articles appearing from 1 January 1950 to 30 June 1956.

[1] The survey of literature pertaining to this review was completed in June, 1956. The author is indebted to Dr. Harris Isbell for many suggestions and for a critical review of the manuscript.

As regards perspective, the review will attempt to evaluate critically the evidence as to whether tolerance and physical dependence, which are generally accepted as characteristics of opiate addiction, are not also characteristics of chronic barbiturate and alcoholic intoxications. Although there are differences in the symptoms of intoxication with, and withdrawal from, each of these drugs, the most impressive thing is not their differences but their similarities [Seevers (5)]. If physical dependence is accepted as being common to all three conditions, a common and simplified principle of detoxification naturally follows. This consists of gradual withdrawal of the drug of addiction, or of some equivalent substitute, in order to prevent the development of severe symptoms of abstinence. Of course, the fact that persons are liable to become addicted to opiates, barbiturates and alcohol under conditions of abuse should in no way preclude the legitimate use of these valuable drugs.

Opiates and Opioids[2]

Relationship of chemical structure to capacity to induce physical dependence (addiction liability).—Potent analgesic action and concomitant addiction liability are associated in six distinct chemical families: the morphine, morphinan, meperidine, methadone, hexamethyleneimine, and dithienylbutenylamine groups [Isbell (6)]. As pointed out by Eddy and co-workers (7), all of the above compounds possess the following chemical features in common: (*a*) a tertiary nitrogen; (*b*) a central carbon atom, none of whose valences is connected with hydrogen; (*c*) a phenyl group, or a group isoteric with phenyl, which is connected with the central carbon atom; and (*d*) maximum activity is obtained when the central carbon atom is connected with the nitrogen by a two-carbon chain. The presence of such a structure does not necessarily mean that the compound will produce dependence. For example, *l*-3-hydroxy-*N*-methylmorphinan is more effective in sustaining physical dependence than is morphine, but the corresponding *d*-isomer is inert [Isbell & Fraser (8)]. The question of isomerism is complex. In the morphinan and methadone series the levorotatory isomers will produce physical dependence and the dextrorotatory isomers will not. In the dithienylbutenylamine series the converse situation prevails [Isbell & Fraser (9)].

When the analgesic potency of a drug in all these six series, as determined in animals, was compared with physical dependence-sustaining potency, as determined in man, some discrepancies seemed to exist which possibly might mean that pain relief and dependence could be separated [Eddy *et al.* (7)]. When analgesic and physical-dependence potency were both measured in man, no such discrepancies were found, with the exception of *N*-allylnormorphine (7). The latter is an outstanding example of a compound which induces morphine-like analgesia (10, 11) but does not produce physical dependence (12) although it is an analogue of morphine (see section on opiate antagonists).

[2] Opioid is a term first used by Acheson & Pfeiffer to designate synthetic opiate-like compounds.

Insofar as methods for ascertaining addiction liability of new compounds are concerned, reliance must still be placed in the procedures developed by Himmelsbach (13) as modified by Isbell (14) and Fraser & Isbell (7, 15) which utilize actively addicted or formerly addicted human volunteers. Methods for determining addictive properties in animals are still not sufficiently reliable to be used without complementary data obtained on patients.

Residual tolerance to opiates.—The question as to whether former opiate addicts show residual tolerance to morphine was investigated by Fraser & Isbell (16). They compared the effects of a single injection of 20 mg. morphine sulfate and a placebo in non-addicts and in opiate addicts who had not received opiates for six months or more. In 20 non-addicts the average maximum fall of rectal temperature was 0.7°C. compared to 0.3°C. in 24 former opiate addicts. The incidence of vomiting was 35 per cent in non-addicts as compared to 12.5 per cent in postaddicts. The effects of morphine on blood pressure, pulse and respiratory rates, and pupillary size were not significantly different in non-addicts and former opiate addicts. These experiments indicate that postaddicts show long-lasting tolerance to certain, but not all, of the effects of morphine.

Relationship of opiate metabolism to tolerance and physical dependence.—Cochin and co-workers (17) and Woods (18) studied the distribution of morphine in several body tissues, urine, and feces of tolerant and nontolerant dogs. Mellett & Woods (19) reported on a similar study in monkeys. They concluded that there is no acceptable evidence that altered distribution or form of morphine (free or combined) is associated with, or responsible for, tolerance or physical dependence. Zauder (20) found that livers of morphine-tolerant rats conjugated the drug more efficiently *in vitro* as compared to control animals, but surprisingly, such animals made tolerant to morphine in other experiments excreted less conjugated drug in the urine.

Tolerance and enzymatic N-*demethylation.*—Axelrod (21, 22) has shown that a triphosphopyridine nucleotide-dependent enzyme found in microsomes of liver of rats *N*-demethylates morphine. The ability of male rats to demethylate morphine is far greater than that of female rats and the rate of demethylation is reduced in males by the administration of estradiol, and increased in the females by testosterone. When male rats are addicted to morphine, the ability of the liver to *N*-demethylate morphine decreases as tolerance is developed and loss of tolerance after discontinuation of morphine is associated with recovery of the capacity of the liver to demethylate morphine. Axelrod (22) notes a parallel between reduction in the rate of *N*-demethylation of drugs by the livers of chronically morphinized rats and cross tolerance between drugs. For example, enzymatic *N*-demethylation of Dilaudid, a compound which shows cross tolerance to morphine, was reduced to about the same degree as morphine, while *N*-demethylation of cocaine, for which no cross tolerance to morphine occurs, was unaffected by chronic morphine administration. Furthermore, the levo-isomers which are active analgesics are *N*-demethylated at two to three times the rate of inactive

d-isomers and *N*-allylnormorphine, an antagonist for opiate drugs, also inhibits *N*-demethylation of these compounds (22).

Treatment of physical dependence on opiates.—This is not synonymous with treatment of addiction, which has been comprehensively reviewed by Isbell & Fraser (1) and Fraser & Grider (23), but involves the simplest phase, withdrawal of drugs. At present, the most rational treatment of physical dependence involves the gradual reduction of the drug of addiction, or else substitution of an equivalent opiate or opioid, and then gradual reduction of the substituted drug. Such treatment mitigates abstinence symptoms without adding to the negligible risk of abrupt withdrawal. Current treatment at the U. S. Public Health Service Hospital at Lexington, Kentucky involves the substitution of methadone, orally administered, for whatever opiate or synthetic analgesic the patient has been using, followed by a reduction in the dosage of methadone over a period of about three to ten days. This method is based upon the facts that methadone is effective orally and will prevent the appearance of signs of abstinence from any known analgesic drug for at least 12 hours. Unfortunately, all of the compounds which are effective in mitigating all symptoms of acute abstinence from opiates are addicting [Isbell (6); Eddy *et al.* (7)]. A variety of drugs not related pharmacologically to morphine will block one or another of the symptoms of abstinence, but only the addicting opiates or opioids will block all of them.

Failure to appreciate the complicated controls required in evaluating treatment of physical dependence leads each year to many misleading reports that new popular drugs are "cures" for morphine addiction. Current examples of such cures are ACTH, cortisone, chlorpromazine, and reserpine. When these compounds were tested on addicts stabilized on known quantities of morphine, all were ineffective in reducing intensity of acute abstinence from morphine [Fraser & Isbell (24, 25)].

Endocrinology of addiction to opiates.—The eosinophil count was studied by Fraser & Isbell (24) during various phases of a cycle of addiction to morphine. When morphine was abruptly withdrawn from addicted patients the eosinophil count began to drop as soon as significant symptoms of abstinence from morphine developed, and when abstinence reached maximal intensity the average eosinophil count approximated zero. When abstinence was terminated by the administration of morphine, the eosinophil count promptly recovered. Neither ACTH nor cortisone reduced the intensity of abstinence from morphine; in fact, both hormones appeared to accelerate the time at which significant symptoms of abstinence developed. During withdrawal of opiates, the pituitary-adrenal mechanism is fully mobilized and administration of ACTH or cortisone in excess of that being provided by the patient's adrenals has no ameliorating effect on the acute symptoms resulting from the withdrawal of morphine. In addicted rats observations which are consistent [Briggs & Munson (26); and Sawyer *et al.* (27)] as well as inconsistent [Sung *et al.* (28)] with those of man have been reported.

Since morphine has long been known to decrease sexual activity in men

and women, and since the animal experiments point to adrenal and gonadal depression via the pituitary (26, 27, 29), Eisenman and co-workers (30, 31) studied the effects of a cycle of morphine addiction on 17-ketosteroid excretion in the urine. Addiction to morphine reduced the excretion of 17-ketosteroids in the urine by 55 per cent. Tolerance to this effect did not develop, and abrupt withdrawal of morphine provoked increases in excretion of 17-ketosteroids of 80 to 500 per cent above addiction levels. 17-ketosteroid excretion returned to pre-addiction levels after three or four weeks. ACTH and gonadotropin administered during morphine addiction elicited responses which were comparable to those observed in the same subjects prior to addiction (31). These experiments show that, although the adrenal and testes may be depressed during addiction, they are capable of responding to specific hormonal stimulation. This suggests that morphine reduces production of ACTH and gonadotropin by depressing the pituitary gland.

Opiate antagonists.—The prototype of compounds of this type is nalorphine (*N*-allylnormorphine). This drug is important because it may be an effective analgesic which does not produce physical dependence, and, in this sense, is not addicting. Furthermore, nalorphine is a specific antidote for poisoning with opiates and opioids and it may be used for diagnosis of the presence of physical dependence.

Nalorphine has only "weak" analgesic effects in small animals (7). In man, however, Lasagna & Beecher (10) and Keats & Telford (11) have shown that nalorphine is approximately as potent as morphine in relieving acute postoperative pain. Like morphine, nalorphine causes respiratory depression, nausea, vomiting, and depression of body temperature, and, in some patients it induces disturbing mental reactions (10, 11, 32, 33). Keats & Telford (11) found that side effects were no more frequent or severe after nalorphine than after morphine in postoperative patients. Lasagna & Beecher (10), however, feel that the side effects of nalorphine are so severe as to preclude its use as an analgesic for routine postoperative use.

Nalorphine is a specific antidote for poisoning with opiates and opioids in both animals and man. Reports are now available on successful use of this drug in cases of human poisoning with morphine, methadone (Dolophine), dihydromorphinone (Dilaudid), methorphinan (Dromoran), meperidine (Demerol) and heroin [Eckenhoff *et al.* (34); Fraser *et al.* (35); Chase *et al.* (36); Bornstein *et al.* (37); and Strober (38)]. Nalorphine appears to be the drug of choice in treating patients poisoned with any opioid. Unlike morphine, nalorphine accentuates or precipitates abstinence from morphine when administered to addicted persons (1, 32). Physical dependence did not develop when nalorphine was administered to nontolerant opiate addicts for 28 to 42 days [Isbell (12)]. Nalorphine, therefore, is a "non-addicting" analgesic, though perhaps not a practical one because of the side effects.

Since *N*-allylnormorphine precipitates abstinence in patients addicted to opiate-like drugs, it may be used to diagnose dependence on opiates [Wikler *et al.* (32)]. A method using nalorphine for this purpose, including

indications, counterindications and precautions, has been described by Isbell (39).

A number of other opiate antagonists have been studied in man by Fraser & Isbell (40). The only significant advantage that any of the agents investigated had over nalorphine was that antagonists of the morphinan series have a longer duration of action and are more effective orally than is nalorphine.

Two general theories have been proposed to explain antagonism of morphine by nalorphine: (*a*) Competition with the opiate for receptor site has been proposed by several investigators, (*b*) Wikler *et al.* (32) postulated that even a single large dose of an opiate induces some degree of physical dependence, and that the antagonistic effects of nalorphine are attributable to the unmasking of this mild physical dependence.

Shaw & Shulman (41) reported that 2,4-diamino-5-phenylthiazole (Daptazole, DAPT) selectively antagonized the respiratory and sedative actions of morphine, but not its analgesic actions. However, Houde & Wallenstein (42) were not able to demonstrate that DAPT antagonized the respiratory depressant effects of morphine.

Barbiturates

In 1914 von Muralt (43) reported a delirium after abrupt withdrawal of barbital from a chronically intoxicated patient. In 1928 Pohlisch (44) reported that convulsions and a delirium followed abrupt withdrawal of barbiturates. In 1949 Isbell *et al.* (45) confirmed these clinical observations by experimentally intoxicating volunteers with secobarbital, pentobarbital, and amobarbital. These investigators were able to show that abstinence from barbiturates was not attributable to an antecedent epileptic or psychotic diathesis or to poor nutrition. Since then it has been generally recognized that the continuous ingestion of large doses of barbiturates over a long period of time will produce physical dependence [Seevers (5); Goodman & Gilman (46)].

Description of barbiturate intoxication and barbiturate abstinence.—Chronic intoxication with large amounts of barbiturates resembles chronic alcoholic intoxication (45, 47). Withdrawal of barbiturates is characterized by an abstinence syndrome which is entirely different from that which follows opiate withdrawal [Isbell *et al.* (45); Fraser *et al.* (47)]. The symptoms may be classified as "minor" and "major." The minor symptoms include (in rough order of appearance) anxiety, involuntary twitching of muscles, coarse intention tremor of hands and fingers, progressive weakness, dizziness, distortions in visual perception (walls seem curved, etc.), nausea, vomiting, insomnia, weight loss, and precipitous drops in blood pressure on standing, or even on sitting. The major symptoms are convulsions of "grand mal" type and a delirium resembling alcoholic delirium tremens. In the first 8 to 12 hours after the last dose of barbiturates, the degree of intoxication gradually declines and the patient appears to be improving. Between the eighth

and thirty-sixth hour the minor symptoms appear and increase in intensity, after which they decline unless the patient develops convulsions, a delirium, or both, in which case tremor, anxiety and insomnia may persist for several days. Untreated cases usually recover in 8 to 14 days. After withdrawal of barbiturates, dramatic changes occur in the electroencephalograms, which consist of either high-voltage paroxysmal discharges or high-voltage paroxysmal activity of a slow type (6 c.p.s. sinusoidal discharges) [Wikler *et al.* (48)]. After a convulsion there is a precipitous rise in serum uric acid followed by a drop in the eosinophil count (47) and a delayed elevation in non-protein nitrogen content of blood. These biochemical changes are not specific since they also follow electrically induced convulsions (47).

Minimal daily dosage of pentobarbital or secobarbital required to produce physical dependence.—The factors possibly affecting intensity of physical dependence on barbiturates may include: (*a*) kind of drug, (*b*) frequency of dosage, (*c*) total daily dosage, (*d*) length of intoxication, (*e*) age, (*f*) sex, (*g*) race, (*h*) personality and (*i*) other individual factors. Of these, definite information is available only on dosage. Fraser and collaborators (47, 49) administered various dosages of secobarbital or pentobarbital to volunteers for 32 to 144 days.[3] After abrupt withdrawal of barbiturates the incidence of abstinence symptoms was as follows: Of 18 patients receiving these drugs in the maximum dose which each could progressively tolerate (0.9 to 2.2 gm. daily) 14 had convulsions, 12 had delirium, and all had minor symptoms of abstinence. In the remaining experiments, all patients received the same dosage throughout the period of intoxication. Of eight patients receiving 0.8 gm. daily, one had convulsions, two had hallucinations, and all had minor symptoms of a degree sufficient to cause therapeutic intervention in a non-experimental situation. Of 18 patients taking 0.6 gm. daily, only two had convulsions, none developed delirium, but nine had minor symptoms of significant degree. Of 18 receiving 0.4 gm. daily, none had seizures or delirium, and only one developed minor symptoms of significant degree. Two patients who received 0.2 gm. of pentobarbital or secobarbital nightly for a year showed no significant signs of abstinence on withdrawal. It was concluded from these studies that, in healthy adult males, a dose of greater than 0.4 gm. of secobarbital or pentobarbital daily is required to produce a clinically significant degree of physical dependence. This is important because it means that physical dependence does not develop when barbiturates are administered in the customary clinical doses. In contrast, chronic administration of opiates or opioids in therapeutic doses produces a significant degree of physical dependence [Lee (50)]. Barbiturates are, therefore, less addicting than opiates in this respect.

[3] "Days of intoxication" refers to time during which patients received the drug under close observation in experimental wards. In the case of patients taking 0.8 grams or more daily, the total days of intoxication would exceed the number indicated in nearly all instances since a majority of these patients were addicted to barbiturates for a variable number of days prior to hospitalization.

The failure of 0.4 gm. daily of secobarbital or of pentobarbital, even though administered for 90 days, to induce a clinically significant degree of physical dependence requires some further comment. Although initially this dosage produced definite intoxication, tolerance developed rapidly (see section on tolerance); consequently "chronic intoxication" was not satisfactorily maintained. By contrast, in the experiment when the dosage was 0.9 to 2.2 gm. daily, the procedure was different in that the dosage was progressively elevated on an individual basis as tolerance developed until each patient was continually receiving the maximum dose compatible with safe ambulatory management. Under these conditions "chronic intoxication" was well maintained and a high degree of physical dependence developed, as witnessed by the high incidence of convulsions, delirium, or both, when barbiturates were discontinued. A dosage of barbiturates sufficiently high to maintain definite impairment of motor coordination seems necessary for the development of a high grade of physical dependence.

Tolerance to barbiturates.—A marked variation in the degree of tolerance is observed in different persons [Fraser *et al.* (47)]. For example, one individual consumed 2.2 gm. of secobarbital daily and even with this enormous intake was able to converse coherently and walk about without staggering, whereas another individual of larger physical proportions was extremely drunk and frequently semicomatose on a daily dose of only 1.0 gm. daily. In most instances a maximum dose of barbiturate could be established for each person, which could not be exceeded by even 0.1 gm. of barbiturate daily without the degree of intoxication becoming dangerously increased. Such critical levels of tolerance are not observed in the case of opiates. The dose to which tolerance can be developed is much greater for opiates than for barbiturates. For example, considerable tolerance may be acquired for a dose of morphine which is 100 times the therapeutic dose (51, 52).

The rate at which tolerance develops when 0.4 gm. of secobarbital or pentobarbital are administered daily was studied by Fraser *et al.* (49). Observations were made on 18 subjects for 30 days prior to, 90 days during, and 14 days after drug administration. Some of the variables measured included visual-hand reaction time and motor coordination, both of which were measured in a semicompetitive situation, and hours of sleep per day. Reaction time and coordination were progressively impaired during the first three days of drug administration, but improvement began on the fourth day, and by the seventh day these functions were nearly normal. During the first ten days of drug administration subjects showed an average increase of 1.68 hours of sleep per day. This declined to an average of 0.99 hours during the second ten days. After 70 days of medication the hours of sleep were entirely comparable to those observed prior to administration of the drug. These experiments show that tolerance to certain effects of barbiturates occurs quite rapidly. Also, tolerance appeared to develop more rapidly in situations where there was some motivation (tests for reaction time and coordinating ability) as compared with situations in which no particular motivation existed (hours of sleep).

Brodie and co-workers (53) demonstrated that after a large dose of thiopental human subjects awaken at plasma levels that are considerably higher than those at which awakening occurs after smaller doses. Since the rate of disappearance of thiopental from the blood of patients receiving high and low doses was comparable, the authors interpret that this probably represents a "tissue" adaptation to thiopental.

There are no direct experiments on the mechanisms of tolerance to and physical dependence on barbiturates. The experimental production of a barbiturate abstinence syndrome including convulsions (54), delirium (55), or both, in dogs and convulsions (56) in cats should now make it possible to attack these problems experimentally.

Treatment of physical dependence on barbiturates.—This has been described fully by Isbell (57), Wikler (58), and Fraser & Grider (23). It consists of stabilizing the addict on the least amount of barbiturates required to induce a mild degree of intoxication, and then gradual reduction of this dose by no more than 0.1 gm. daily. In the reduction treatment any of the barbiturates commonly used in medical practice may be substituted for whatever barbiturate the patient is using. Pentobarbital is a convenient drug to employ since its length of action is intermediate. The treatment outlined above has been shown to be effective, whereas other treatments such as substituting chlorpromazine and reserpine for barbiturates have not been proved effective and safe. The diagnosis of barbiturate addiction should always be borne in mind if a patient suddenly develops convulsions, a toxic psychosis or both. If such cases are not recognized and properly treated, a fatality may ensue [Meyer (59); Fraser *et al.* (60)].

Alcohol

The problem of tolerance to and physical dependence on alcohol has been thoroughly reviewed by Jellinek (61) and more recently by the World Health Organization of the United Nations, Expert Committee on Alcohol and Alcoholism (62, 63). Several pertinent references to the problem of tolerance are included in the review by Jacobsen (64).

Physical dependence on alcohol.—Bowman and co-workers (65) stated that few cases of delirium tremens occurred in 10,000 admissions of alcoholics to Bellevue Hospital, even though alcohol was abruptly discontinued. Although evidence such as this appears impressive, it is not conclusive. A large proportion of the alcoholics admitted to general hospitals have been intoxicated for only a brief time. Therefore, they would not be expected to develop serious manifestations of abstinence after abrupt withdrawal of alcohol [Isbell *et al.* (66)]. Furthermore, as Kalinowsky (67) has pointed out, even though alcohol is withdrawn, such patients are almost invariably given some type of sedative medication such as paraldehyde, barbiturates, or chloral hydrate. Such medication might amount to substitution of drugs with equivalent effect to that of alcohol. Also, total withdrawal of alcohol may not be necessary for precipitation of abstinence since, as in the case of barbiturates,

merely a reduction in the dose of alcohol may be sufficient to precipitate such symptoms (66).

Victor & Adams (68) studied 266 patients who were consecutively admitted to the Massachusetts General Hospital for treatment of alcoholism. After intake of alcohol was stopped, 92 of the 266 patients had acute alcoholic tremulousness, 30 had tremor and transitory hallucinations, 6 had acute auditory hallucinosis, 14 had typical delirium tremens, 11 had atypical delirious-hallucinatory states, and 32 had "rum fits" (convulsions). Victor & Adams considered that all of the above syndromes were attributable to abstinence since they were able to relate them, in most instances, to cessation or reduction of drinking. Other syndromes which were not related to abstinence included acute alcoholic intoxication (56 patients) and nutritional diseases such as Wernicke-Korsakoff's neuropathy (eight patients). Forty-nine patients showed miscellaneous symptoms which could not be definitely attributable to abstinence. Victor & Adams also pointed out the remarkable similarity of the symptoms of abstinence from alcohol and those of abstinence from barbiturates.

Isbell and co-workers (66) gave ten male former morphine addict volunteers 266 to 489 ml. of 95 per cent alcohol daily for 7 to 87 days. The objective was to maintain each subject continuously in the maximum state of alcoholic intoxication which was compatible with safe ambulatory management for a period of at least six weeks, and then to discontinue alcohol abruptly. Alcohol was given orally at intervals of one to two hours from 6 a.m. to 12 midnight, with supplementary drinks at 2 a.m. or 3 a.m. Four patients, who withdrew from the experiment after 34 or less days of drinking, had only mild symptoms after discontinuation of alcohol. The duration of "chronic intoxication" in these 4 subjects was considered insufficient for a high degree of physical dependence to develop. Six of the 10 patients drank for 48 to 87 days. Convulsions and delirium did not develop in any of the subjects during the period of chronic alcoholic administration. Following abrupt withdrawal of alcohol, all six patients who drank for more than 48 days developed tremors, marked weakness, nausea, vomiting, diarrhea, hyperreflexia, fever and hypertension. Two of the six patients had seizures, three had a frank delirium, two had transient visual or auditory hallucinations and one escaped both convulsions and hallucinations. These phenomena occurred despite the ingestion of an adequate diet, which contained multiple vitamin supplements, throughout the periods of intoxication and withdrawal.

These experimental studies in man [Isbell *et al.* (66)] confirm the clinical studies of Kalinowsky (67), Goldberg (69, 70), Sheps (71), and Victor & Adams (68) to the effect that physical dependence on alcohol develops in chronically intoxicated persons and that one cause of delirium tremens is abstinence from alcohol. This perspective is fortified by the production of an abstinence syndrome (severe tremulousness, convulsions, and a "canine delirium") when alcohol was abruptly withdrawn from chronically intoxicated dogs [Fraser, Isbell & Eisenman (72)].

Tolerance to alcohol.—Chronic alcoholic intoxication does induce a limited

degree of tolerance. For example, three patients of Isbell *et al.* (66) were markedly intoxicated and had blood alcohol values of over 200 mg. per cent on the tenth day of chronic intoxication with alcohol when they were consuming from 397 to 466 ml. of 95 per cent ethyl alcohol. Eleven days later, after 21 days of chronic intoxication, they were able to consume the same amount of alcohol without having clinically significant amounts of alcohol in the blood and without any clinical evidence of intoxication. The decline in blood alcohol levels when the same dose of alcohol is maintained has been designated "metabolic" tolerance. The margin, however, between the doses associated with low blood alcohol levels and sobriety and the doses associated with high blood alcohol levels and drunkeness is small. Raising the alcoholic intake in these same subjects from between 397 to 466 ml. daily to between 430 to 479 ml. resulted in a return of high blood alcohol levels and drunkenness.

Goldberger (70) found evidence for "tissue" tolerance to alcohol. Subjects who were chronic drinkers made better performance scores in a variety of tests than did abstainers, when both groups were observed under the condition of similar blood alcohol values. Similarly, Isbell *et al.* (66) and Wikler *et al.* (73) showed "tissue" tolerance in respect to the degree of drunkenness and electroencephalographic patterns, when these were evaluated at the beginning and the end of the experiment under the condition of equivalent concentrations of alcohol in the blood. Newman & Lehman (74) have described a similar phenomenon in dogs.

Mechanism of convulsions and delirium in abstinence from alcohol.—As in the case of the convulsions which occur during abstinence from barbiturates, there are no experiments with direct bearing on the mechanism of convulsions and delirium in abstinence from alcohol. However, Fraser *et al.* (72) have produced an alcoholic abstinence syndrome in dogs. This should make possible an experimental approach to the problem of mechanism. Flink *et al.* (75) and Suter & Klingman (76) believe that a low concentration of magnesium in the serum may play a role in delirium tremens.

Treatment of physical dependence on alcohol.—This is the simplest phase of therapy. The manifold psychiatric problems and the many associated pathologic changes which are involved, particularly those of a nutritional nature, will not be considered here. It is possible to withdraw alcohol completely and abruptly, but, as in the case of dependence on opiates and barbiturates, it is wise to substitute a drug with effects equivalent to those of alcohol in order to avoid convulsions, delirium, or both. Several of the barbiturates, paraldehyde and chloral hydrate are potent central nervous system depressants and may be substituted for alcohol, and then gradually withdrawn. The above sedatives have been given routinely in treating alcoholics for many years, but the physicians using them have not always realized that such symptoms as anxiety, insomnia, weakness, tremulousness, and even convulsions and hallucinations, are usually caused by lack of alcohol rather than by its direct toxic effects. Confusion on this point has arisen in part because symptoms appear very rapidly after drinking has stopped and because

complete cessation of drinking is not necessary to precipitate abstinence. Early appearance of symptoms is attributable to the relatively rapid metabolism of alcohol (as compared with most opiates and barbiturates) and to the fact that definite symptoms of abstinence appear at blood alcohol values of 85 to 100 mg. per cent (66, 72). In fact, severe symptoms, including convulsions, may appear as early as 12 hours after the last drink (66). Complete cessation of drinking is not necessary to provoke abstinence since a reduction of 25 per cent in the average daily intake of alcohol will result in a fall of blood alcohol values to zero (66). Acceptance of the concept that abstinence from alcohol causes the symptoms makes it obvious to the clinician that it is necessary to administer sedatives in adequate dosage to prevent symptoms of acute withdrawal from alcohol, then to reduce gradually the dose of the sedative over a period of days. When new drugs, such as chlorpromazine (77) or meprobamate (78), are advocated to prevent or treat delirium tremens, the clinician, being aware that physical dependence on alcohol is an important feature of the disease, will be better prepared to evaluate such new therapies.

Conclusion

It is generally accepted that chronic administration of opiates or opioids leads to tolerance and physical dependence, with the precipitation of a characteristic abstinence syndrome when they are discontinued abruptly. The preponderance of evidence now indicates that if barbiturates or alcohol are taken under conditions of chronic abuse, tolerance and physical dependence develop, and a characteristic abstinence syndrome (which differs from that of the opiates) develops when alcohol or barbiturates are discontinued abruptly. Since physical dependence is common to all three intoxications, a common and simplified principle of detoxication naturally follows. This consists of gradual withdrawal of the drug of addiction, or of some equivalent substitute, in order to prevent the development of severe symptoms of abstinence.

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EXPERIMENTAL RETROLENTAL FIBROPLASIA[1]

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Careful control of oxygen administration to premature babies has now proved so effective in preventing retrolental fibroplasia that the disease becomes of less and less significance, and, to the clinician, will soon be no more than a closed chapter, whereas the question of the mechanism by which oxygen influences immature retinal vessels appears increasingly complex, and, to the laboratory worker, assumes growing importance. This year's ophthalmic survey is therefore devoted to experimental studies on the effect of oxygen on the immature retina, work which has arisen directly or indirectly from the problem of retrolental fibroplasia, and which has grown to such proportions that there will be no opportunity here to include an appreciation of the valuable contributions of clinical investigators.

The Role of Hyperoxia

The first animal experiments dealing with the effect of exposure to high concentrations of oxygen on the immature eye were reported by Coxon (1) who exposed newborn rabbits to hyperoxia but failed to produce retrolental fibroplasia. However, her reason for choosing the rabbit, "because anatomically and developmentally . . . it closely resembles the human," was unfortunately mistaken. The first animal experiments showing the injurious effect of high oxygen on the immature eye were those of Gyllensten & Hellström (2) who subjected about 50 newborn mice to intermittent exposures of pure oxygen. About one-third of the animals showed ocular hemorrhages, retinal folding, and vitreous organization. They did not, however, report proliferation of the retinal vessels, which is the first stage of retrolental fibroplasia, and the changes they observed, as they later demonstrated more fully, were largely attributable to the organization of hemorrhages in the primary vitreous body originating from persistence and proliferation of the hyaloid artery and tunica vasculosa lentis. These changes are apparently peculiar to the rat and mouse and are not seen in the kitten or in the premature baby. Indeed, with the exception of the hyaloid artery, these structures are no longer present in the viable premature baby.

No further observations of this kind appeared in the literature until Ashton *et al.* (3) reported their discovery that oxygen in high concentrations was able to exert an obliterative effect on the ingrowing vessels of the kitten retina. When the animal was returned to air, the vessels only partially reopened, and vascularization then recommenced from the disc region to

[1] The survey of literature pertaining to this review was completed in August, 1956.

invade the retina and extend into the vitreous. Thus a pathologic process was produced which was almost exactly comparable to the early stages of retrolental fibroplasia, and the authors emphasized the significance of these changes in the genesis of the disease in man. That the injury occurred in two phases: (*a*) vaso-obliteration in oxygen, and (*b*) vasoproliferation in air appeared to resolve many of the conflicting opinions regarding the etiology of the disease.

This report was followed by the experimental studies of Patz *et al.* (4) who, working independently, had produced the vasoproliferative changes of the oxygen effect. In a purely histologic study they observed capillary proliferation extending into the vitreous from the retinae of newborn mice, ratlings, kittens, and puppies exposed to 60 to 80 per cent oxygen for varying periods. Gyllensten & Hellström (5), who meanwhile had been continuing their previous studies, then reported that transfer of the newborn mouse to air after oxygen exposure (in contrast to their original experiments using intermittent oxygen exposure) also resulted in a pathologic proliferation of retinal vessels into the vitreous. Further confirmatory evidence of vasoproliferation following oxygen exposure in mice was provided by Gerschman *et al.* (6).

Although La Motte (7), Patz *et al.* (8) and Huggert (9) had specifically noted attenuation of the retinal vessels during administration of oxygen to premature infants, the vaso-obliterative effect of oxygen as a selective phenomenon peculiar to growing retinal vessels as described by Ashton *et al.* (3) did not find experimental confirmation until a year later, when it was observed also by Patz (10) in flat preparations of injected retinae of rats, kittens and dogs, and by Gyllensten & Hellström (5) in sections of mouse eyes. Michaelson *et al.* (11) regarded the absence of capillaries in the retinae of newborn mice kept under hyperoxic conditions from birth as attributable to inhibition of capillary formation rather than to vaso-obliteration. These experiments, however, cannot be compared with those previously reported, for they show the influence of hyperoxia on the development of retinal vessels from their commencement at the disc, whereas vaso-obliteration can be demonstrated only when retinae already containing growing vascular complexes are exposed to hyperoxia. Furthermore, these workers failed to produce pathologic neo-vascularization by the method they employed, and their speculation that diminution of capillary growth may be the basis of retrolental fibroplasia seems unwarranted.

Experimentation on retrolental fibroplasia has in the main been carried out by three groups of workers: Gyllensten & Hellström in Sweden, Patz and co-workers in America and Ashton and co-workers in Great Britain. Their findings are remarkably in accord but it is important to note that each group has concentrated on different laboratory animals, the first on mice, the second mainly on rats (though also on mice, puppies, and kittens) and the third on kittens. This species difference should be taken into account in considering such variations as exist in their experimental findings.

So far it is known that high concentrations of oxygen at atmospheric pressure are able to obliterate the ingrowing vessels in the developing retina of the kitten, puppy, ratling and newborn mouse, animals which all have a retinal vasculature similar to that of man both anatomically and developmentally. In the newborn rabbit, wherein the vascular arrangement differs considerably, the effect is much less marked and the vasoproliferative phase does not occur [Ashton *et al.* (3)].

Direct observation of the living retinal vessels is essential for the thorough study of the vaso-obliterative phenomenon, and this so far has been carried out experimentally, by a new technique, only in the case of the kitten [Ashton & Cook (12)]. In this animal the process commences as a marked constriction of the arteries and arterioles; the arterioles and the arterial side of the capillary circulation are the first vessels to obliterate, and this process is followed by the disappearance of the whole capillary bed; then the main arteries and finally the main veins close, leaving an apparently avascular retina. Injected specimens show that in general this process begins peripherally, that is, in the region where the growing vessels and the retina itself are most immature; it then spreads posteriorly, the disc region being the most resistant and the last area to be completely obliterated. This phenomenon is confined to the growing retinal vessels, occurring neither in the other vessels of the eye, nor in those of other organs [Patz (10) Ashton *et al.* (13)], nor in growing vessels as observed in the rabbit cornea [Ashton & Cook (12), Michaelson *et al.* (14)], in the rabbit ear chamber [Ashton & Cook (12)], in chick embryos, nor in cat or rat embryos [Ashton (15)]. Nor apparently can the embryo be affected by administering oxygen to the pregnant animal; in three experiments in which pregnant cats were placed in high concentrations of oxygen during the last four, six and seven days of gestation respectively, the eyes of the offspring were completely unaffected [Ashton (16)].

In the kitten, Ashton *et al.* (13) found no histologic changes, other than vaso-obliteration, as a result of oxygen exposure. Even after 26 days of continuous exposure to 70 to 80 per cent oxygen there was no evidence of retinal degeneration. Similarly Gyllensten & Hellström (5) noted only one or two hemorrhages and retinal folding, apart from absent retinal vessels, in mice exposed to 98 to 100 per cent oxygen for periods ranging from 2 to 16 days. Both groups of workers apparently agree that the visual cells remain structurally intact. These observations contrast strongly with the recent report of Noell (17, 18), that exposure of adult rabbits to concentrations as low as 60 per cent at ambient pressure resulted in selective irreversible destruction of the visual cells after seven days of exposure.

As regards the histologic changes to be seen in the retina after oxygen exposure and transfer to air, Ashton *et al.* (13) showed in kittens that an intense angioblastic activity developed in the inner layers of the retina with extension of vaso-formative tissue and delicate new vessels into the vitreous, but there was no apparent degenerative change in the retinal neural elements

and no retinal detachment. Later, multiple acute-angle folding developed in the retina and this persisted even when the angioblastic activity had subsided and the retina had otherwise returned to normal. An animal in which complete revascularization of the retina had been induced by oxygen vaso-obliteration appeared to have normal vision two years later.

Thus in the kitten, angioblastic activity occurred only in the period in air following hyperoxia, but Patz (10) in his early experiments observed the proliferative retinal changes in mice during continuous oxygen exposure and without transfer to air. Ashton *et al.* (13) believed this to be caused by an unsuspected fall in oxygen concentration in the blood, either through variation in ambient concentrations or through pulmonary complications, a view supported by the work of Gyllensten & Hellström (19) who have since shown that proliferative changes may develop in the mouse retina in continuous oxygen, providing the concentrations fall to low levels.

As regards long-term oxygen exposure Hellström (20) has recently described in detail a number of degenerative histologic changes to which previous reference had been made [Gyllensten & Hellström (5, 21)]. Mice were kept intermittently in oxygen (98 to 100 per cent for three days followed by air for three days) for periods of one to three months. At the end of this time the retinae showed severe atrophy, most pronounced in the mid-periphery. Ganglion cells were few, the inner plexiform layer thin, and the inner nuclear layer reduced to one or a few rows of cells, often fused with the outer nuclear cells. In the most severe cases the visual cells also showed atrophy. Localized folded detachment of the retina with pigment cell proliferation occurred in some instances, and the authors compared the picture to that seen after mono-iodoacetate injection (actually it is more typical of the sodium iodate effect). Similar retinal folding was also reported by Ashton *et al.* (13) as a late feature of the vasoproliferative phase, but the atrophic changes have not so far been observed in the kitten in either hyperoxia or in the subsequent transfer to air.

Various factors are known to influence the vaso-obliterative and vaso-proliferative phases of oxygen exposure, and these will now be considered individually.

Degree of maturity of retinal vessels.—The severity of the vaso-obliterative effect of oxygen is inversely proportional to the maturity of the retinal vessels. Once the retinal circulation is fully established and the normal vascular architecture attained, oxygen fails to produce significant obliterative changes and has no structural effect whatsoever on the vessels of the adult cat.

Recent experimental work, however, suggests that this is probably not a function of vessel immaturity alone but of a changing retinal metabolic environment. For instance, it has been found possible, by exposing kittens of different ages to oxygen and transferring them to air, to produce retinal vasoproliferations which differed only in that with one group of animals the new vessels were growing in a retina of an age normally sensitive to oxygen,

and in the other group in a retina of an age normally insensitive to oxygen.[2] Re-oxygenation showed that vaso-obliteration of these abnormal proliferations occurred only in the first group, thus demonstrating that vaso-obliteration is the outcome of an interaction between oxygen and retinal metabolism and not a peculiar reaction of growing retinal vessels themselves [Ashton (22)]. That oxygen fails to affect growing vessels elsewhere in the body is a concordant fact. It is probably not without significance that the degree of sensitivity to oxygen is also inversely proportional to the development of the visual cells [Pedler (23)].

Similarly vasoproliferation on transfer to air is indirectly related to the maturity of the retinal vessels since its features differ according to whether the vaso-obliterative effect in oxygen was complete or partial. In the kitten, when total vaso-obliteration has been produced in oxygen, revascularization recommences from the disc region and forms a profuse circular ingrowth of vessels several layers deep, without definition into the normal three complexes and with numerous glomerular proliferations into the vitreous. This new ingrowth gradually differentiates into arteries and veins and the intravitreal vessels disappear, the changes occurring in a postero-anterior direction. After about five months the retina has completely revascularized, but the general architecture differs considerably from the normal, there being as many as 20 main vessels issuing from the disc region, compared with the normal three groups. Apart from arcading in the retina, described above, the histologic picture of the retina returns to normal. Retinal detachment does not occur.

When vaso-obliteration in oxygen has been partial, revascularization does not commence from the disc region, but the new vessels originate from the whole field of unobliterated vessels and from such vessels as have reopened. In the least sensitive age-groups where vaso-obliteration occurs only at the periphery or anterior portion of the retina, the subsequent vasoproliferation is similarly confined and no proliferations occur posteriorly.

In studies of retinal vasoproliferation, Patz (10, 24) and Gyllensten & Hellström (21) agree that the animal's eye is susceptible to oxygen only when the retina is incompletely vascularized and is resistant once vascularization is complete, but in their experiments they had not related the proliferations to the preceding degree of vaso-obliteration, to which the variable responses are fundamentally attributable.

Duration of exposure to hyperoxia.—In injection experiments Ashton

[2] Example of Experiment

Age of kitten	Hyperoxia	Air	Vasoproliferation in Retina
1 day	4 days	10 days	15 days old (immature)
10 days	15 days	10 days	35 days old (mature)

et al. (13) found that vaso-obliteration was dependent upon the period of exposure to hyperoxia; it was moderate in 12 hours, severe in 24 hours and total in 36 hours. However, these were injected retinae so that the findings actually indicate the degree of irreversible obliteration after graded periods of exposure rather than the extent of closure before injection. It is, however, of interest that obliteration is irreversible after 24 to 36 hours, and the exact time relationships of the phenomenon have been found in direct observation experiments [Ashton & Cook (12)]. It occurs in two phases, immediate and delayed. An immediate effect consists of severe constriction of the large vessels, and obliteration of the capillaries develops after five minutes exposure to hyperoxia. The vessels then dilate again after about ten minutes and so remain, although in continuous oxygen, for about six hours when the delayed effect comes into operation. This results in a gradual total vaso-obliteration, and once it is achieved the circulation may be either opened or closed, in each case in about five minutes, by alternating air and oxygen. Ashton *et al.* (13) have found in kittens that obliterated vessels remain closed as long as the animal is kept in 70 to 80 per cent oxygen (this has been shown for periods of over three weeks) provided pulmonary complications do not occur.

With regard to vasoproliferation in air, the relationship to longer periods of oxygen exposure is not entirely clear. The evidence of Ashton *et al.* (13) suggests that vasoproliferation is more marked when the period of vaso-obliteration in oxygen is more prolonged, but since there is some degree of variation in response in individual animals the findings were inconclusive. Patz *et al.* (4) found that ocular lesions in mice increased with the number of days in oxygen, but it is doubtful whether this was solely attributable to hyperoxia. Further information is required on this aspect of the problem, for it is of importance in deciding whether the vasoformative factor may elaborate and accumulate in hyperoxic conditions. The weight of evidence so far available is against this, since the factor is probably not formed in these conditions or may possibly be antagonized by oxygen.

Concentration of oxygen.—It is clearly of importance to know the exact concentration of oxygen which may be harmful to the developing eye, and this has been investigated by Ashton *et al.* (13), Patz (24) and Hellström (25). The first group of workers, using the kitten, found that the severity of the vaso-obliterative effect of oxygen was directly proportional to the concentration of oxygen, but that concentrations below 35 per cent had little or no effect in the most sensitive age-groups. The differences in degree of vaso-obliteration over and above a critical level of oxygen, however, are not great, as shown by recent direct-observation experiments in which it was found, using the delayed effect, that closure occurs gradually over a range of 40 to 45 per cent oxygen with no effect below that level and complete closure above [Ashton & Pedler (26)]. Patz (24) found in the rat that oxygen concentrations under 40 per cent did not appreciably constrict or obliterate

the retinal vessels at any age. In the mouse, Hellström (25) found that a concentration under 40 per cent caused no detectable histologic changes. At 40 per cent an injury of the eyes could be demonstrated in relatively few cases. This occurred following both short and long exposures, covering both vaso-obliterative and vasoproliferative phases of the oxygen effect. With concentrations of 50 per cent and over, the incidence of eye injury rapidly increased.

It would thus appear that oxygen in concentrations below 40 per cent is probably innocuous to normal immature animals, but the margin of safety is a narrow one.

Influence of retinal detachment.—By direct observation of the retinal vessels, Ashton & Cook (12) found that if the retina became detached in the course of the experiment then vaso-obliteration in the retina could no longer be induced and, conversely, that obliterated vessels re-opened when detachment developed. In a subsequent paper they showed that detachment of the developing retina prevents the vaso-obliterative action of oxygen even though a normally effective ambient concentration is maintained for as long as four days [Ashton & Cook (27)].

In view of these observations Ashton & Cook (28) studied the effect of retinal detachment on normal vessel growth in the retina without oxygen exposure. It was found that detachment in the developing kitten retina led to a downgrowth of retinal vessels beyond the inner nuclear layer, frequently penetrating the retina completely and forming a network on its outer surface. Vessels also extended into the vitreous to form glomerular tufts exactly similar to those found after oxygen exposure in the attached retina. Retinal detachment in the adult animal, however, had no such influence.

It is evident, therefore, that close apposition between retina and choroid is essential both for the obliterative phenomenon to operate and for the normal development of retinal vessels, but whether this is attributable to inadequate diffusion or impaired transfer of oxygen, or to differences in reactivity to oxygen between the attached and detached retina, has not yet been determined.

Sympathectomy.—Patz (24) showed in puppies that section of the sympathetic trunk had no effect on either the vaso-obliterative or vasoproliferative phases of oxygen exposure. Similarly, Cook & Ashton (29) found in kittens that cervical sympathectomy had no influence either on the immediate or delayed stage of vaso-obliteration. Nor was the delayed stage modified by adrenergic blockade with N-(2-chloroethyl) dibenzylamine (Dibenamine). Hence, sympathetic innervation is probably not concerned in the mechanism of oxygen injury to the immature eye.

Concentration of carbon dioxide.—The addition of 5 per cent carbon dioxide to high concentrations of oxygen has been shown to have no influence on oxygen vaso-obliteration or upon subsequent vasoproliferation in air [Ashton *et al.* (13), Patz (24), Hellström (30)]. This fact further distinguishes

the localized phenomenon of vaso-obliteration from the generalized vasoconstrictive action of oxygen, which is known to be nullified by the dilating action of carbon dioxide [Wolff & Lennox (31), Cobb & Fremont-Smith (32), Cusick *et al.* (33)]

Mode of transfer to air following oxygen exposure.—Whether retinal vasoproliferation can be modified by gradual lowering of oxygen concentration ("weaning") as compared with direct transfer to air, is a question of considerable clinical interest [Bedrossian *et al.* (34, 35), Szewczyk (36)] which has so far received no conclusive answer in experimental work. Gyllensten & Hellström (19) studied this problem in mice and concluded that weaning could retard but not prevent oxygen changes.

Theoretically an argument could be advanced in favor of weaning, for if oxygen is regarded as antagonistic to the vasoformative factor, the transfer of an animal to a concentration of oxygen above normal but below the level producing obliteration (40 per cent) should modify the exuberance of vessel growth without prolonging vaso-obliteration. Unpublished experiments by Ashton (37) in which seven-day-old kittens were subjected to five days of 70 to 80 per cent oxygen, followed by three days of 35 to 45 per cent oxygen, followed by four days of 30 to 35 per cent oxygen and compared with a control group subjected to 70 to 80 per cent oxygen and transferred direct to air, showed no difference in the degree of vasoproliferation. In another group of kittens treated in the same way but allowed to survive in air for a further 18 days the largest outgrowth seen was in one of the weaned animals. There is thus no experimental support for the clinical practice of weaning and, as regards the premature baby, the question must remain open, for since the dangers of oxygen have become known, further clinical experimentation to check the existing evidence would be quite indefensible.

Effect of re-oxygenation.—In view of the well-attested clinical claims that oxygen is of value in the treatment of retrolental fibroplasia [Jefferson (38), Szewczyk (39), Bedrossian *et al.* (34), Manschot (40)] it is of interest to consider experimental work on the effects of re-oxygenation. Ashton *et al.* (13) returned kittens in the vasoproliferative phase to the same conditions of hyperoxia as those which originally caused vaso-obliteration, and also studied the subsequent effect of a second return to air after the two periods of oxygen exposure. Although a return to hyperoxia could to some extent control vasoproliferation, the inevitable return to air was accompanied by an exacerbation of the process which was attributable to the effects of the further period in oxygen. Furthermore, on the theoretical grounds already outlined in the previous section, kittens in the vasoproliferative phase have been returned to innocuous levels of hyperoxia, e.g., 35 to 40 per cent, but although there appeared to be some attenuation of the intraretinal proliferations, those in the vitreous were completely unaffected [Ashton (41)]. It would appear that once irreversible vaso-obliteration has occurred in oxygen, vasoproliferation must follow sooner or later when the avascular retina returns to air despite episodes of re-oxygenation. Thus it

has not been possible to demonstrate in the laboratory animal the alleged therapeutic value of a return to oxygen in retrolental fibroplasia.

State of nutrition.—Since only a proportion of premature infants develop retinopathy following oxygen exposure, and since the human disease differs from the experimental lesions, it has been thought that a number of other factors may be contributory. Among these the state of nutrition was thought to be of importance [Lubchenco *et al.* (42)], but Hellström (43) is the only worker to have specially investigated this possibility experimentally. He showed in the mouse that both normal and abnormal vasoproliferations were depressed by starvation. Oxygen-induced proliferations, however, became more frequent in animals starved in oxygen but allowed to regain weight in air. In ratlings, Campbell (44) had noted a reduced rate of retinal vascularization with a decrease in the rate of body growth, and Michaelson *et al.* (11) had found an inhibition of oxygen-induced vaso-proliferations in under-developed mice. This inhibition of vascular growth in relation to impaired nutrition is exactly as would be expected, and the accentuation of angioblastic activity after a period of starvation may be explained by postulating an accumulation of the vasoformative factor while growth response continued to be inhibited by sub-nutrition.

The Role of Hypoxia

There would seem to be little doubt that the vasoformative reaction of the retina, on transfer from high oxygen concentrations to air, is attributable to retinal hypoxia from inadequate blood supply, the latter arising through obliteration of the retinal vessels caused by the oxygen exposure. It might be expected, therefore, that conditions of general hypoxia could directly initiate retinal vasoformation without previous oxygen exposure. Indeed, the fact that cases of retrolental fibroplasia have been reported which have not received supplemental oxygen [Coxon (45), Dancis *et al.* (46), Bembridge *et al.* (47)] requires explanation, and it has been suggested that a generalized hypoxia, as may result from anemia, hyaline membranes [Ingalls (48)], or interstitial plasma-cell pneumonia [Manschot (49)], may directly cause the disease. There is little clinical evidence and no convincing experimental evidence to support this view, for in general hypoxia vasoformation is not stimulated to a sufficiently severe degree. Clinically, the number of anoxic infants not developing retinopathy is far more impressive than the few cases attributed to anoxia, especially since many of these cases have at some time received oxygen, e.g. those of Manschot (49). Experimentally, Ashton *et al.* (13) exposed kittens to continuous hypoxia of 10 to 15 per cent oxygen (the lowest level the animals could tolerate), Patz (24) reared newborn mice and rats in 10 to 14 per cent oxygen for 21 days, and Gyllensten & Hellström (50) exposed newborn mice to 3 per cent oxygen intermittently for 22 days. None of these workers succeeded in producing vasoproliferative changes similar to those found in retrolental fibroplasia. The claim of Mizukawa (51) to have produced changes similar to retrolental

fibroplasia in rats subjected to low barometric pressures for seven days is the only contrary experience.

It has been suggested, therefore, that low oxygen concentrations consistent with survival are not able to induce a sufficiently severe degree of retinal hypoxia in the developing eye to give rise to abnormal vasoproliferation [Ashton (52)], but the degree of drainage permitting accumulation of the vasoformative factor is probably also of great importance. Since the vessels remain open in a retina subjected directly to hypoxia, any such factor would be rapidly removed; on the other hand hypoxia secondary to oxygen vaso-obliteration provides the necessary local conditions for excessive vascular growth.

Relationship Between the Experimental and Human Disease

The close similarities between the vasoproliferations occurring in the early stages of retrolental fibroplasia and those produced experimentally in animals have been analyzed in detail elsewhere [Ashton (53), Ashton *et al.* (13)], and the causative role of oxygen is today so well established, especially since control of supplemental oxygen has led to the virtual disappearance of the disease, that it would be more appropriate now to consider the differences between the animal and human lesions.

The main divergence is in the course of their development, for while the vasoproliferations in the premature infant frequently (but by no means inevitably) progress to retinal detachment and cicatrization, they regress in the animal eye and retinal detachment does not develop. Of the hundreds of experiments carried out on newborn animals of different species, only two puppies with extensive vitreous hemorrhage have developed detachment [Patz (10)]. Thus, while there is a close experimental analogue of the vasoproliferative phase of retrolental fibroplasia, there is none of the cicatricial stage. This important difference has not been under-estimated, and both Ashton (15, 54) and Hellström (20) have emphasized the need for caution in interpreting the findings in infants and animals since there are clearly differing factors involved.

On the other hand, an exact reproduction of human disease in laboratory animals is not to be expected, especially in this case where there are anatomical differences between the eye of man and that of the animals used. Moreover, although the eye of the full-term mouse, rat, kitten, and puppy matures after birth, these animals are not, of course, premature in any other sense. Several reasons for the failure of detachment have been considered. In the rat and mouse it has been attributed to the relatively large lens [Patz (10)], and in kittens to the presence of a tapetum or to the rarity of hemorrhages in the experimental lesion [Ashton (52)]. However, it is noteworthy that even the very earliest stage of vasoproliferation in the baby and newborn animal differ in an important respect. In the human retina the vasoformative tissue extending into the vitreous contains a dominant fibroblastic element, and the contraction of this tissue as it extends to form fibrous bands

is mainly responsible for detachment. Moreover, the presence of such tissue in the vitreous establishes a nutritional requirement which perpetuates the accompanying vascular growth. In the newborn animals the vasoformative tissue contains few or no fibroblasts and consists of endothelial cells and delicate new vessels which, having responded to the limited quantity of vasoformative factor diffused from the retina, gradually atrophy. These differences probably depend on minor variations in the normal process of vascularization in the two types of retinae. Whether this is the explanation or not, it serves to show that additional factors to oxygen exposure in the genesis of oxygen-induced retrolental fibroplasia need not necessarily exist, for lack of identity in the experimental disease can be explained solely on species variation.

The reported occurrence of retrolental fibroplasia without oxygen exposure, however, remains a problem, the importance of which is gradually emerging as the oxygen-induced form comes under control. It already appears to be a rarity, of much less significance than was once supposed, for in many centers where oxygen is not adequately controlled, retrolental fibroplasia, at least in its irreversible stages, is no longer seen. The cause of such isolated cases as have been reported, and their relationship to the oxygen-induced form, has not yet been defined.

Mechanisms of the Oxygen Effect

The pathologic changes so far described have been related to ambient concentrations and not to actual blood-levels of oxygen. It has, however, been shown by platinum electrode recordings that variations in ambient concentrations are reflected at the retinal surface even when the retinal vessels have been severed [Patz (55)]. In the vitreous humor similar changes in oxygen tension occur, but a greater quantity of oxygen diffuses into the vitreous when the animal is under severe hyperoxia than under moderate hyperoxia, although basically the same amount of oxygen is being carried through the blood vessels in both conditions [Goren & Krause (56)]. The reason for this is unknown but whatever the explanation may be, the hypothesis that vaso-obliteration is attributable to raised oxygen tensions within the retinal tissue through increased diffusion from the choroid is now completely acceptable. How hyperoxia obliterates growing vessels, however, is obscure; it may be caused by the elaboration of a vasoconstrictor substance or by the removal of a vasoformative factor.

There is considerable evidence that oxygen is of fundamental importance in the control of normal retinal vascularization. The capillary-free zone around the arteries and the avascularity of the outer layers of the retina adjacent to the choroid both point to such a conclusion, which is reinforced by the modifications which may be induced experimentally, i.e., narrowing of the periarterial capillary-free zone by lowering oxygen tensions [Campbell (44)], its widening with raised oxygen tensions [Ashton *et al.* (13)] and vascularization of the outer retina by detachment [Ashton & Cook (28)]. That

oxygen tensions above the normal range should close developing retinal vessels, and that concentrations below it should excessively stimulate their growth, appear therefore as manifestations at either extreme of a single normal process. Since it is evident, as previously shown, that some metabolic process peculiar to the immature retina is involved, the varying vascular responses, both normal and abnormal, suggest that such a metabolism must be governed by oxygen concentrations, and there would seem little reason for postulating a separate or abnormal mechanism to explain the more severe manifestations.

There is clearly an urgent need for metabolic studies comparing the immature and mature retina, and the effect of oxygen upon the various enzyme systems concerned, for until the very recent work of Hellström (57) no such work had been published. He investigated the *in vitro* metabolism of the retinae of oxygen-exposed ratlings, but the differences observed between oxygen-exposed and control animals were small and insignificant, both concerning oxygen consumption and anaerobic glycolysis. However, the vaso-obliterative effect of oxygen is particularly labile, as shown by its rapid reversal after retinal detachment, and these negative findings in retinae excised post mortem can only indicate the absence of more permanent metabolic changes. So far Hellström (58) has found no evidence of a change in the localization of succinic dehydrogenase in the retinae of animals exposed to hyperoxia. Barron (59) has recently emphasized that sulfhydryl compounds and sulfhydryl enzymes are more sensitive to the action of high oxygen pressure than other oxidative-reduction systems and other enzymes. On exposure to oxygen at atmospheric pressure he considers it possible that the aerobic metabolism is inhibited. Ashton (60) has been unable to prevent vaso-obliteration with agents known to be effective against oxygen toxicity, such as β-mercaptoethylamine and 2,3-dimercaptopropanol. Nor has Pedler (61) succeeded in duplicating the action of oxygen with agents having similar toxic effects through a common basis of action, such as X-irradiation [Gerschman *et al.* (62)]. Electrophysiologic studies are also proving of value [Noell (17, 18), Hellström (63)] but it is as yet too early to attempt an assessment of these various findings.

The extensive proliferation of retinal vessels after oxygen exposure suggests the accumulation of a vasoformative factor which is probably the product of a metabolic process preponderating in the immature retina; it accumulates when drainage is impaired and would seem to be a metabolite produced in hypoxic circumstances. In this connection anaerobic glycolysis should be especially considered [Ashton & Cook (28), Brehme (64)] for its rate in the retina is unique among normal tissues, being equalled only by by that of tumors [Warburg *et al.* (65)]. It is of interest, however, that oxygen has no obliterative effect on growing vessels in transplanted malignant tumors in rats [Ashton & Pedler (66)], but it will be remembered that the vulnerability of the retina to hyperoxia depends also upon its structural relationship to the choroid.

Much work remains to be carried out in elucidating these intricate questions, which now extend far beyond the original problem of retrolental fibroplasia, but their answers promise exciting advances in ocular physiology and pathology.

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PEDIATRICS[1,2]

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The reviewer of a field as broad as pediatrics cannot hope to produce a comprehensive report. Limited by space assignment and by his own ability to read, comprehend, digest, and evaluate the productions of the year, he must be selective. In order to summarize briefly those articles of particular interest to the author, it has been necessary to omit many significant papers and, indeed, to slight sizeable areas which fall within the pediatric purview. It is hoped and anticipated that many of these deficiencies will be rectified by coverage in other reviews of the current series.

Poliomyelitis

Few medical events have commanded such widespread public interest as the vicissitudes of the poliomyelitis vaccination program of 1955. Hopes for a successful preventive raised high by the Francis report (1) in April, were quickly undermined by the recognition of poliomyelitis in children inoculated with Cutter vaccine and in the household contacts of such children. At the end of April the National Poliomyelitis Surveillance Program was established within the Public Health Service. A report (2) from this unit provides facts essential to an understanding of the events of this memorable year. In all, 204 cases of poliomyelitis were accepted as being associated with the use of Cutter vaccine. One-third of these were traced to two lots of vaccine and, because of the pattern of vaccine distribution, 70 per cent of the cases occurred in California and Idaho. Approximately three-fourths of the victims had paralysis. In those individuals whose disease followed their own vaccinations, the incubation period fell between the fourth and fourteenth days, and paralysis generally appeared first in the inoculated extremity. Individuals infected by household or community contact showed incubation periods ranging from eight to 28 days. Virus (Types I and III) was isolated from some of the lots of Cutter vaccine but not from a specimen of Wyeth vaccine which was under suspicion.

After a temporary suspension of the vaccination program, a revised set of safety standards was imposed. The theoretic and practical problems of production of an effective and safe vaccine were thoroughly reviewed by Salk (3) and by Scheele & Shannon (4). The adequacy of the new standards is attested by the Surveillance Program (2) which states that no evidence has been adduced to incriminate any lot of vaccine used between July and November, 1955. Although some cases of poliomyelitis occurred in vac-

[1] The survey of literature pertaining to this review was completed in June, 1956.

[2] The following abbreviations are used in this review: BCG (Bacillus Calmette Guérin); RLF (retrolental fibroplasia).

cinated individuals during this period, three-fourths of them were non-paralytic, and very few occurred within 30 days of vaccination.

The report further submits data which measure the efficacy of the vaccine in large groups of vaccinated and unvaccinated children held under simultaneous continuous observation in 11 states and one city. In each of the groups, the attack rate of paralytic poliomyelitis among the unvaccinated children was two to five times the rate in the vaccinated group. Differences in the attack rates for non-paralytic poliomyelitis between the two groups were variable or non-existent, a peculiar phenomenon noted also in the Francis (1) report which still lacks an adequate explanation. An interesting comparison of the age distribution of paralytic cases between the years 1952 and 1955 was made on data submitted from 21 states for the earlier year and from 33 states for the current year. Curves constructed for the age specific attack rates were almost identical in shape with the notable exception of the portion of the 1955 curve for the ages seven to nine years, the age group which received primary attention during the vaccination of school children. A pronounced dip in the curve at this point suggests a distinct effect of the vaccine on this age group.

An independent report from Massachusetts (5) describes the spread of a severe epidemic of Type I poliomyelitis from Boston outward into the rest of the state. From the timing and pattern of spread, it is concluded that the small amount of Salk vaccine used in Boston could not have been responsible for initiating the epidemic. The attack rate among children who received one dose of vaccine was less than half the rate among the unvaccinated; for those who received two or more doses, the rate was reduced to one-third. These figures corroborate the approximate efficiency of the vaccine as stated in both the Francis report and the report of the Surveillance Program.

Efforts to develop a vaccine by feeding live but avirulent virus are continuing. In two studies (6, 7) during the year, live virus which has been shown to have little or no pathogenicity for experimental animals even when injected directly into the nervous system has been fed to human subjects. Intestinal infection with virus excretion in the stools and the development of favorable antibody titers have been demonstrated without the appearance of clinical illness in the subjects. The virus strains used are segregated by tissue culture passage from known strains or are isolates from the stools of healthy children. Further study will be required to determine whether this type of vaccination can be expected to provide a uniformly safe and enduring immunity.

Although the vaccination program occupied the spotlight, a number of articles appeared during the year which add significantly to our understanding of the manner in which the poliomyelitis virus invades the body and how it is disseminated within the community. Some of these latter epidemiologic studies will become difficult to repeat when vaccination of the child population has been widely applied.

In spite of a sharp increase in the volume of studies made possible by the

new tissue culture techniques, there is still some disagreement about the exact mechanism of virus invasion and propagation within the human body. Faber has presented his views derived from many years of study in a monograph (8) and a briefer summary (9). He emphasizes the neurotropism of the virus and regards the peripheral nerves of the oro-pharyngeal-intestinal tract with their subtendent ganglia as the main point of invasion, the site of early multiplication, and the channels of spread of the virus. Appearance of virus in non-neural tissues such as tonsils, Peyer's patches, intestinal mucosa, lymph nodes, and the blood stream are viewed as secondary or late phenomena. Critical for the infected individual is the extent to which virus spreads centripetally along the nervous network before the infection burns itself out or is halted by a defense mechanism. This latter point constitutes the most significant divergence of his theory from the more widely held view that central nervous system invasion depends upon the transport of virus from non-neural tissue via the blood stream.

Bodian (10), using evidence obtained from virus isolates from tissues of orally infected chimpanzees, proposes a schema of virus invasion with lymphatic tissue (tonsils, Peyer's patches) as the primary site of early multiplication. Dissemination of virus proceeds thence both externally into the pharyngeal secretions and feces and internally into cervical and mesenteric lymph nodes. The third step consists of passage of virus through the lymph nodes and into the blood stream, and the final step is the transport to target organs, particularly the central nervous system.

Sabin's concept of pathogenesis (11) based upon currently available information is more complex but more flexible than either of the above theories. The epithelium of the gastrointestinal mucosa is regarded as the major locus of virus multiplication and excretion. From this portal of entry, virus spreads to and sometimes multiplies within the regional lymphatic structures. Thence in smaller amounts it may invade the blood stream and be transported to other non-neural tissue where secondary foci of multiplication may be set up. From these latter and from the originally invaded intestinal mucosa, the nervous system may be invaded through peripheral nerve endings which conduct virus to the local autonomic and sensory ganglia and in some instances centripetally to other areas of the central nervous system. The extent of nervous tissue invasion depends upon the titer of virus in non-neural tissue, upon the restraining influence of antibody present in the host, and upon the degree of neurotropism of the individual virus strain.

Isolation of virus from peripheral lymph nodes of patients dying of poliomyelitis is reported by Wenner (12) in 12 out of 15 attempts. The small amounts of virus recovered at a time when serum and tissue antibodies were present in low titer only, led him to the conclusion that these lymphatic structures were secondarily infected during the viremic phase of the disease and did not represent a focus of active virus multiplication.

Results obtained during the first 27 months of a long term epidemiologic study of poliomyelitis in Louisiana households have now been reported (13)

by Fox and his associates. Three groups of families with dissimilar geographic and economic status are under continuous surveillance. The families are selected through the appearance of a newborn infant on whom monthly stool specimens for virus isolation and blood specimens for antibody determination are obtained. Members of the household are similarly studied annually and more frequently when the index infant yields evidence of recent poliomyelitis infection. To date, evidence for infection has been obtained in 109 out of the 161 index infants. First infections occurred most frequently during the months of July and August. The presence of maternally transmitted antibody was confirmed, but it had generally disappeared by three months of age and was not always able to prevent infection of the very young infant. Large family size and poor economic status were found to be associated with early infection of the infant. Within a given household the infection was seen to spread to all of the previously non-immune members. Re-infection occurred only in individuals whose previous antibody titers were low, and these individuals excreted virus only briefly, if at all. The study reaffirms the high rate of contagion of poliomyelitis virus among household contacts and points again to non-immune children as the main vectors of infection. Only about one-third of the laboratory-detected infections were associated with minor illness, and there were no instances of paralytic disease.

The contagiousness of poliomyelitis within households is also emphasized by detailed studies of two epidemics of Type I infection (14, 15). From either virus isolations from stool or throat washings, or through antibody responses it was shown that 75 to 100 per cent of the susceptible children under fifteen years of age become infected when virus is introduced into the household. Adults within the home and casual contacts without show evidence of infection with somewhat less frequency. Once again, the young susceptible child is identified as the chief vector in the spread of virus.

In paradoxic contrast, Wehrle (16) has found that poliomyelitis victims infected with Type I or Type III strains present little risk to the personnel of the hospital. Even susceptible adults working with such patients are adequately protected in part by the isolation techniques used and in part by the fact that the infectiousness of the disease has already declined by the time the patient gains admission to the hospital.

Ramos-Alvarez & Sabin (17) cultured stool specimens from large numbers of children in Cincinnati, Mexico City, and Vera Cruz during the months of July and August in an attempt to determine the incidence of cytopathogenic agents. Among Cincinnati children, the incidence of poliomyelitis virus recoveries was of the order of 0.5 per cent, but in the Mexican children the incidence ranged from 3.4 to 8.2 per cent. In the children between one and two years of age in Vera Cruz, the recovery rate was 12 per cent. In each of the groups studied there was a much higher recovery rate of ECHO (enteric cytopathogenic human orphan) viruses. The pathogenetic significance of this latter group of agents remains to be determined. They apparently can-

not be regarded as the viral counterpart of the normal bacterial flora of the stool since they disappear with advancing age of the host.

A comprehensive review of the subject of immunity to poliomyelitis by Sabin has appeared during the year (18).

Newborn and Premature

Studies of respiratory physiology and pathology approach the core problem of "hyaline membrane disease" from several different salients. Observations of respiratory rates (19, 20) by two independent groups are in essential agreement although the data are presented with different emphasis. Normal full-term infants respire at a steady rate of about 40/min. with a standard deviation of less than ten. Prematures and those with poor prognosis from impending hyaline membrane syndrome or other respiratory disease have initial or rapidly rising rates of 60 or more per minute. Sustained tachypnea of this degree is suggested as a means of identifying infants with poor outlooks and of gauging the effect of therapeutic measures. Blystad (21) using a microtechnique has measured CO_2 and CO_2 tensions and CO_2 contents of the bloods of prematures (*a*) without respiratory disease, (*b*) with clinically suggestive but non-fatal hyaline membrane disease, and (*c*) with fatal and pathologically verified hyaline membrane disease. If the method is reliable (the reviewer does not feel competent to judge), marked increases in CO_2 tension paralleled the symptoms and severity of the disease. In fatal cases the values were about double the normal and there was a drastic drop in calculated pH which in many instances fell well below 7.0. The decline in oxygen tensions was significant but less drastic. Taken with an observation of Miller (22) that newborns do not respond with hyperventilation after brief periods of anoxia, Blystad's findings suggest that the driving force for the hyperpnea observed in hyaline membrane disease is the CO_2 accumulation rather than anoxia.

Inquiries into the nature and pathogenesis of the hyaline membrane itself now seem to agree that a chief component is fibrin derived by exudation from the infant's pulmonary circulation. The material in the lungs of infants dead of the disease has been stained by Gitlin & Craig (23) with fluoresceinized antibodies specific for human fibrin. Stevenson & Laufe (24) produced membranes in guinea pigs by intratracheal instillation of human plasma and amniotic fluid and concluded that the latter supplied thromboplastic substance necessary for the conversion of fibrinogen to fibrin. Lynch (25, 26, 27) in a series of papers offers a welter of evidence and theory which left the reviewer stimulated but confused. He too appears to believe that exudation from the pulmonary circulation occurs but that it also carries with it hemoglobin derived from lysed red blood cells. Metabolic, circulatory, and neural disturbances are included in his complex discussion of the initiating mechanism. Theorizing from previously recorded information about the hyaline membrane syndrome, Lendrum (28) suggests that the pathogenesis begins with relative left-sided heart failure when the myocardium is unable to ac-

cept the stress of conversion from fetal to adult circulation because of immaturity or the effects of cesarean section, or maternal diabetes, or toxemia. He regards the extreme congestion of the pulmonary circulation as much more important than the occurrence of membrane. He thinks the latter derives from exuded blood proteins which are concentrated by evaporation and absorption of water.

In a controlled study involving two hundred premature infants, Silverman (29) reports that no therapeutic benefits could be ascribed to the use of nebulized water vapor in the incubators when compared with the results obtained with the 90 to 100 per cent humidity resulting from the standard operation of the isolette. Schaffer (30) has called attention to the importance of pre-partum or intra-partum pneumonia as a source of paranatal mortality and emphasizes the importance of prophylactic administration of antibiotics to mothers and infants when the amniotic membranes have been ruptured prematurely.

The Medical Research Council (31) has set forth the results of a study of the incidence of retrolental fibroplasia (RLF) in seventeen British premature units for an eighteen month period during 1951 to 1953. Among 1,095 prematures who survived at least two months, the incidence of retinopathy was found to be 7.7 per cent, and of blindness 4.1 per cent. Extensive correlations of various aspects of maternal and fetal factors led to the conclusion that the number of days in oxygen was the chief determinant of the incidence of RLF. Another survey from England and Wales for the year 1951 (32) reports an incidence of cicatricial RLF of 1.8 per cent among nearly 7,000 infants traced. No cases were found among prematures reared at home. In the United States, the Bellevue group (33) states that rigid curtailment of oxygen in their nurseries by the use of tanks containing mixtures of oxygen and nitrogen which make it impossible to administer more than 40 per cent oxygen has eliminated cicatricial RLF among the last five hundred prematures. Mortality rates rose slightly during this period but the increase was not statistically significant.

In the hope of finding a better prognostic index and therapeutic guide for infants with hemolytic disease of the newborn, several groups of workers (34, 35, 36) have studied the serum pigments by spectrophotometric analysis. In addition to bilirubin, which has already been extensively used as an indicator of the severity of the process, and hemoglobin, which may be an artefact in the collection of specimens, attention is drawn to a heme pigment (methemalbumin) with an absorption band close to 415 mμ. This compound is stated to be hematin which has been released during intravascular hemolysis and which has become associated into a complex with serum albumin. Two of the groups (34, 35) believe that the concentration of this pigment early in the course of the disease may provide a better method of discovering cases with poor prognosis; the other group (36) regards it as an unreliable index of prognosis. The possibility is suggested that hematin present in large amounts may combine with albumin and thus

exclude bilirubin from a similar association, leaving it free to diffuse out of the vascular spaces and combine with neural tissue. Further study seems indicated before this pigment can be fully evaluated.

A report from Sweden (37) discusses the occurrence of obstructive jaundice during hemolytic anemia, considers its mechanism, and emphasizes the accompanying difficulty in depressing bilirubin levels by exchange transfusion.

Bowman (38) finds that isohemagglutinins A, B, and D are absorbed from the gastrointestinal tract of the newborn in amounts too minute to detect except when very large quantities are fed. Presumably, mothers may be permitted to breast feed newborns affected by mild erythroblastosis.

Further information was recorded during the year which indicates that kernicterus is not exclusively a complication of iso-immunization. Brown & Zuelzer (39) found excessive bilirubinemia in a group of 30 infants whose major blood groups excluded the possibility of iso-immunization. Both term and premature infants were included and among the latter one infant died with kernicterus. They were unable to determine the cause of hyperbilirubinemia except to suspect that it was an exaggeration of the process which causes "physiologic" icterus. They advise exchange transfusion when blood levels exceed 20 mg. per 100 ml. in the hope of forestalling neurologic disorders. A survey of autopsies performed by the Atomic Bomb Casualty Commission in Japan (40) revealed 25 instances of kernicterus among Japanese infants. With two possible exceptions, Rh-iso-immunization could be excluded. One case was clearly related to A-antigen. Incomplete evidence is presented to exclude ABO-iso-immunization in the remainder, but from the parents' blood groups it seems highly improbable that more than half of the victims could have been so affected. About three-fourths of these infants were premature.

Two aspects of the medical care of prematures have been implicated in the production of kernicterus. The administration of large doses (30 mg./day) of vitamin K (41) resulted in bilirubin blood levels on the fifth day of life in excess of 18 mg. per 100 ml. in over one-third of the infants under study, whereas only one infant in twenty-five responded in this fashion when the dose was limited to 1 mg. on the first day of life. Within the group receiving high dosage of vitamin K, two infants died of kernicterus and three others suffered suspicious clinical symptoms but recovered. This study supports suspicions which have been voiced in correspondence with the *Lancet* (42, 43). During a survey of the effectiveness of various antibiotic regimens used in their premature nursery over the past several years, Silverman and his colleagues (44) discovered a significant association between the use of penicillin and sulfisoxazole therapy and the occurrence of kernicterus among infants who failed to survive. Since penicillin was used in some of the other antibiotic regimens, suspicion must be directed either at sulfisoxazole alone or in combination with penicillin.

Interesting observations on the fate of Fe^{55} received by newborn infants

through the placental circulation are related by Smith *et al.* (45). Computations indicated that at one year of age 70 per cent of the hemoglobin iron of the infant was still iron which had been obtained transplacentally from the mother. By two years of age, 40 per cent could be traced back to the maternal source, and 90 per cent of the total iron originally transferred to the infant was still in use as part of the body hemoglobin. It was also shown that iron obtained from the diet was scarcely used by the term infant before the age of three to four months. Iron obtained in his original blood pool or from other tissue stores conferred before birth was used in preference up to this age. Among premature infants, dietary iron was used earlier after birth.

A study of hematologic values in small premature infants (46) confirms previous observations that progressive decline in hemoglobin and red cell levels continues until eight to nine weeks of age and is not influenced by iron administration or by vitamin B_{12} and chlortetracycline. The authors believe it is safe to allow such infants to become quite anemic (down to levels of 5 gm. per cent hemoglobin) without transfusion so long as they are well otherwise, a sharp reversal of policies in force only a few years ago when persistent efforts were thought necessary to keep hemoglobin levels up.

Determination of gamma globulin levels in a group of 140 infants during the first two years of life (47) has confirmed previous studies upon smaller numbers of subjects. The newborn starts with a level which is equal to or even higher than his mother's, but suffers a progressive decline during the first three months of life, reaching values of approximately one-third of the initial level. During this period he is apparently unable to fabricate gamma globulin of his own. Ingestion of colostrum during breast feeding has no effect upon the rate at which the levels fall. After three months, endogenous synthesis appears to commence and the level rises gradually. Gamma globulin concentrations behave quite independently of the other plasma protein fractions.

A review of the problem of bacteremia in the newborn (48) demonstrates that a high level of clinical suspicion and use of broad-spectrum antibiotics can result in a favorable outcome for infants so afflicted. A change from the streptococcal and staphylococcal infections in former years to infections with the enteric group of organisms is noted. No entirely satisfactory portal of entry of the infection can usually be determined.

Figures from the Boston Children's Hospital (49) demonstrate that meconium ileus in the newborn is not necessarily a fatal disease nor associated with later severe cystic fibrosis of the pancreas. Over one-fourth of the infants operated upon since 1945 have survived operation, and a number of these have done well on medical management of their cystic fibrosis. In addition, a few infants are described who recovered from mild meconium ileus without surgical intervention.

Vargas, Levin & Santulli (50) discuss perforation of the stomach in the newborn and report eleven cases. Congenital defects of gastric muscle, peptic

ulceration, sepsis, and trauma caused by tube feeding were among the underlying causes. The disorder was seen most frequently in premature infants. Two infants survived surgical repair of the defect.

From South Africa comes a report of a small epidemic of myocarditis in infants five to seventeen days of age (51). Based upon the local prevalence of Bornholm disease, the findings of acute interstitial myocarditis in autopsied infants, and the isolation of virus from the stools of one and the myocardium of another infant, the authors believe that they have observed the first epidemic of Coxsackie Type B infection in the newborn. Since this virus produces fatal illness only in newborn mice, it would be reasonable to suppose that its effect might be severe in the newborn human infant yet benign in the older child and adult.

Neoplasia and Surgical Disorders

Roentgen therapy of the head, neck and chest during infancy and early childhood has been suggested as an incitant to neoplasia in later life. Tracing some 1,400 infants who received radiation for enlarged thymus glands, Simpson, Hempelmann & Fuller (52) found a greater incidence of leukemia, thyroid carcinoma, osteochondroma and thyroid adenoma than among untreated siblings or the general population. Clark (53) uncovered a history of radiation therapy in all thirteen children in his series. The minimum dose of radiation was 200 r for the affected children in each of these groups (except for some of the leukemia victims in Simpson's report). Uhlmann (54) contests the validity of this association on the grounds that his series of children with thyroid carcinoma contained only four out of 25 who had been previously irradiated, and raises the additional objection that the amount of radiation reaching the thyroid gland is scarcely in excess of that received during a chest fluoroscopy. The task of pursuing this important lead is complicated by the long interval between radiation treatment and the discovery of carcinoma (average of seven years in Clark's series). The Mayo Clinic (55) affirms a rising incidence of carcinoma of the thyroid in recent years but offers no information about prior radiation therapy. Winship & Chase (56) have collected 285 examples of thyroid carcinoma in children from the literature and by questionnaires. They discuss pathology, incidence, geographic distribution, and prognosis. An association with radiation therapy is stated, but the evidence is not given in convincing form.

The uncommon but interesting association of thrombocytopenic purpura with large hemangioendotheliomata is discussed by Good (57). In a study of three cases the theory is advanced that some peculiarity of the growth of the tumor (insufficient blood supply, altered metabolism, teleologic destruction) makes a sudden demand upon the infant's supply of platelets in order to form widespread platelet thrombi within the tumor. The bone marrow examination reveals changes similar to those observed in idiopathic thrombocytopenic purpura with a shift to the left of megakaryocytes and an

increase in their numbers, but failure of platelet release. Splenectomy had little effect upon the thrombocytopenia in two of the cases and in several of those reported in the literature, whereas radiation and destruction of the tumor was followed by a rapid increase in platelets. The main hazard to such patients lies in the danger of excessive hemorrhage either into the tumor or elsewhere before platelet levels are brought under control. In another case report Meeks (58) states that radiation of the tumor mass did not elevate platelet levels while splenectomy did.

Fatal nephritis following radiation therapy after removal of a Wilms' tumor is reported by Grossman (59). His review of the literature indicates that the kidney is relatively resistant to the effects of radiation. Other instances of radiation nephritis have been observed, however, after dosages in excess of 2,000 r to an inadequately shielded kidney.

Edmondson (60) has compiled a handy source of information on tumors and cysts of the liver and bile ducts. His article reviews the literature and attempts to classify these relatively uncommon disorders.

Accumulated clinical experience with a number of surgical conditions affords an opportunity to gauge prognosis, to evaluate the effects of operative treatment, and to improve the understanding of pathogenetic mechanisms.

Gross (61) delineates the principles of management of undescended testis at the Children's Hospital of Boston evolved from observation of more than 1,200 cases. He advocates delay in operation until prepubertal years in the hope of spontaneous descent, unless an associated hernia demands correction. He does not favor the use of hormone therapy, nor of the Torek procedure. The latter is criticized because of its tendency to place undue and unyielding traction upon the spermatic cord which may compromise the blood supply of the testis after operation. Instead, careful mobilization of the cord to allow maximum descent of the testis and the application of an elastic type of traction is recommended. Studies conducted upon 38 cases of bilateral undescended testicle in this group demonstrated potential fertility in 79 per cent.

An analysis of the 99 cases of acute hematogenous osteomyelitis seen at the Grace-New Haven Community Hospital during the past 30 years (62) points out the declining incidence, improved prognosis, and change from surgical to medical management which has occurred since the introduction of penicillin. Since material from the local lesion is not available early in the illness if at all, repeated blood cultures are urged in order to identify the infecting organism. Over 60 per cent of the cases analyzed were attributable to staphylococcal infection, about 18 per cent to streptococcal infection. Mortality among infants is no greater than among older children. The strong propensity for sequestra to be absorbed during infancy leads the authors to advise conservatism even with large segments of necrosis.

Koop (63) records the experience of the Philadelphia Children's Hospital with the management of neuroblastoma and "malignant ganglioneuroma." He states that fourteen months is the crucial survival period for children

with this malignancy. He advocates as widespread surgical removal of the tumor as feasible without block dissection of invaded organs aside from the kidney. In spite of metastasis to liver or lymph nodes, 12 of 19 patients so treated have survived. He discounts radiation therapy as an important factor in survival. No patients with lung or bone metastasis survived.

Since 1951, an increasing number of cases of severe emphysema of a single pulmonary lobe have been described in newborn and young infants. Early recognition and surgical removal of such lobes usually results in prompt relief and full recovery. The mechanism leading to this progressive emphysema has not been clear. Survey of the surgical specimens in seven cases by Bolande (64) revealed hypoplastic bronchial cartilage in two, inflammatory stenosis in one, external compression by a ductus arteriosus in another, and no bronchial abnormality in three. All specimens revealed microscopic alveolar fibrosis with excessive deposition of collagenous connective tissue in the supporting stroma of the lobe. It is suggested that a developmental abnormality of the connective tissue which makes the lobe more rigid and less elastic than normal is the primary cause of emphysema rather than partial obstruction of the bronchial lumen. Another report (65) describes the notable absence of luminal obstruction but finds deficiency of cartilage in peripheral portions of the bronchial tree.

A comprehensive discussion of gastroesophageal abnormalities about the cardia of the stomach is given by Swyer (66). The embryology, diagnosis, and management of these uncommon conditions are considered in detail.

Ravitch (67) advises operative correction of pectus excavatum for cosmetic reasons. He describes the operative technique used on 50 patients of all ages with a single fatality due to wound infection. He recommends early operation for infants with severe deformities.

Endocrine Disorders

The problems of ambisexual development are discussed in a significant group of papers which approach the topic from the endocrine (68), surgical (69) and psychiatric (70 to 73) points of view. Of particular interest is the close agreement among the several authors upon the general principles of diagnosis and treatment which should be followed. No less than seven variables require consideration in determination of sex: (*a*) genetic sex determined by sex chromatin studies, (*b*) gonadal sex determined by surgical exploration and biopsy, (*c*) morphology of the intermediate ducts determined by laparotomy or urethroscopy, (*d*) anatomy of the external genitalia, (*e*) the hormonal influences which control the secondary sex characteristics, (*f*) the sex which has already been assigned to the individual, and (*g*) the individual's subjective image of himself and his erotic impulses, designated the "gender role". Accurate diagnosis depends upon information obtained under the first five of these headings. Practical management of individuals beyond the stage of infancy demands careful consideration of the psychologic implications of assigned sex and gender role. The latter

appears to be conditioned by the environmental attitudes surrounding the child during its early years. When the individual has been reared consistently and unambiguously as a member of one sex, the corresponding gender role is determined early in life so that it is considered unwise to alter the assigned sex after the age of two years. Inasmuch as assigned sex and gender role may not agree with the appearance of external genitalia or secondary sex characteristics, it is highly desirable to reach a firm and accurate decision about the sex in which the child is to be reared before the end of infancy.

When sexual abnormality is discovered in the small infant, the most pressing concern is to determine whether or not the adrenogenital syndrome is present. This, the most common form of ambisexuality, can be diagnosed without surgical intervention if urinary 17-ketosteroids are distinctly increased and pregnanetriol can be demonstrated in the urine. Blood sodium and potassium levels should also be determined since a deficiency of electrolyte-regulating hormone, which is present in some infants with the adrenogenital syndrome, requires prompt treatment with salt and deoxycorticosterone. When the adrenogenital syndrome is diagnosed in an infant with pseudohermaphroditism the course of action is clear; the female sex is confidently assigned, cortisone is given to halt or limit virilization, and later surgical correction of the external genitalia is projected. The adrenogenital syndrome in males begins with precocious puberty rather than anatomic abnormalities of the genitalia.

When abnormalities other than the adrenogenital syndrome are discovered in infancy, early, thorough investigation is advocated. In assigning sex to such an infant the usual objective is to achieve concordance between the appearance of the external genitalia as modifiable by future surgical procedures, and the assigned sex. Ablation of gonads and later hormone therapy can aid in the approximation of sexual normality. Considerations of genetic sex are given small weight by the authors. Psychologic studies show that genetic sex has no apparent bearing upon the type of gender role developed by the individual.

As indicated above, caution must be exercised in changing the assigned sex when abnormalities are discovered after infancy. Psychologic disturbances created by shifting the gender role are usually of serious nature. Discordance between genetic sex and assigned sex is usually not revealed to either the parent or the child.

A surprisingly favorable degree of mental health was found among the ambisexual individuals examined. As one might expect, more of the prepubertal individuals were adjudged emotionally healthy than were those who had matured and were required to face the social implications of their abnormal anatomy. Notwithstanding, a high percentage was found to be in reasonably good emotional adjustment, even in some instances where discordance between external appearance and assigned sex existed. This most interesting set of papers opens up many speculations regarding the nature

of sex and the relationship between biologic and psychologic aspects thereof.

Reviews of the adrenogenital syndrome (74) and discussion of the probable metabolic abnormality or abnormalities responsible (75) have appeared during the year.

Two tabulations of the results of treating hypothyroid children (76, 77) stress the importance of early diagnosis and consistent, adequately controlled treatment. Ultimate intelligence, which at best appears to fall somewhat below that of the child's coevals, is most seriously threatened among infants whose symptoms begin before the age of six months and in whom adequate therapy is delayed.

Information about the late results of the medical management of hyperthyroidism is becoming available (78, 79). With some few exceptions (poor co-operation, suspicious nodules, drug toxicity, persistent goiter) the antithyroid drugs appear to be capable of inducing satisfactory remissions. Recurrence of hyperthyroid symptoms may be precipitated by infection or emotional disturbance, but such remissions generally respond to a resumption of therapy. Simultaneous administration of thyroid appears to promote reduction in gland size. Normal growth and uneventful puberty without exacerbation of the disease are reported for a number of the patients. The duration of therapy needed to provide an adequate remission varies with individual cases but is seldom less than two years.

Infectious Disease

The management of diphtheria is becoming a forgotten art over most of the United States, yet in some areas of the South it still presents a significant problem. Beach (80), while evaluating erythromycin as an antibiotic, emphasizes the importance of diphtheria antitoxin as a *sine qua non* of therapy. Among 43 cases, one death from myocarditis occurred. Erythromycin in doses of 25 to 50 mg./kg./day was generally but not universally effective in eradicating *Corynebacterium diphtheriae* from throat cultures. No important toxic manifestations were observed.

Jaffe (81) discovered 100 cases of clinically mild but bacteriologically confirmed pertussis in Washington, D.C. within a four month period. Nearly 80 per cent of the affected Negro population had received routine pertussis immunization. Vaccination did not appear to have either an ameliorating effect upon the severity of the disease nor did it decrease the secondary attack rate within families. The relatively poor protection thus demonstrated is charged to the use of vaccine of low potency.

Another attempt has been made (82) to determine the relation between asthmatic bronchitis in infancy and chronic respiratory disorders in later life. Partly by recall examination and partly by questionnaire, the respiratory fate of more than two hundred infants who had been hospitalized with asthmatic bronchitis during the first year of life was determined. Among them, the incidence of persisting asthma was more than three times, and

the incidence of recurrent bronchitis was more than five times the rates found in the general population of school age.

Valuable data on bronchiectasis are contained in a comprehensive review of more than 200 children (83) followed for periods of two to 15 years. In a surprising 40 per cent, the disease had its inception during the first year of life usually in the wake of pneumonia or bronchitis. The predilection for the left lung and for the combined middle and lower lobes of each lung is noted. Cures or great improvement were obtained in about three-fourths of the children surgically treated either by lobectomy or pneumonectomy. Poor results were encountered among children who had asthma in association with their bronchiectasis.

Children who are unable to fabricate gamma globulin offer a rare opportunity to dissect the process of resistance to infection and to assess the role of circulating antibody. Good (84) reviews the literature and emphasizes the absence of plasma cells and their failure to appear in the local exudate during the course of pulmonary disease. His dictum that such children fail mainly in their resistance to bacterial infections and are able to withstand viral infections is partially controverted by a report of progressive vaccinia (85) in a child whose plasma contained no gamma globulin. In the latter instance, lesions in the lungs are also described as containing plasma cells. The fortunate rarity of agammaglobulinemia constricts the ability to test associations of this sort.

Evidence in support of a theory that toxoplasmosis is transmitted to man by the ingestion of pork from infected swine is presented in an article by Weinman & Chandler (86). Serologic and skin test data reveal a high rate of infection in man which rises from low levels in childhood to 30 to 70 per cent during middle age. Rats, swine, and primates can be infected orally and it is presumed that man, too, could suffer from the ingestion of viable parasites. A survey of antibody titers in locally slaughtered, garbage-fed hogs confirmed the presence of high antibody titers. No isolates of toxoplasma from pork offered for food consumption are reported, but the theoretical possibility is discussed that parasites might survive through the processes of slaughtering, storing, and cooking. Positive association of trichinella immunity and toxoplasma immunity in man is noted together with a low rate of immunity among orthodox Jews.

The geographic prevalence of histoplasmosis is delineated by Manos and his colleagues (87) by estimating the percentage of positive histoplasmin reactors among lifetime residents of various counties in the central United States. A high prevalence of sensitivity was found in the triangular area with apices at Columbus (Ohio) Memphis, and Kansas City. Silverman (88) has reviewed the literature on histoplasmosis and presents his findings in seven fatal cases of the disease.

A valuable article by Smith (89) considers the incidence, diagnosis, and modern management of acute bacterial meningitis.

Miscellaneous

From a study of more than 500 unselected newborn infants Caffey (90) states that neither the traditional roentgen nor physical methods of diagnosis will permit accurate prediction of congenital dislocation of the hip in infants under the age of six months. Acetabular angles were determined at birth and again at six and 12 months of age. The variations were so wide at birth as to defy prognostic usage. Furthermore, there was a pronounced decrease in the width of the angles as the infants grew. Matching of skin folds, extra skin folds, and limitation of abduction were equally useless as prognostic indices. Caffey believes that treatment of "potential" dislocation of the hip should be abandoned. As a by-product of this study (91) it was discovered that mongoloid infants have narrow acetabular and iliac angles at birth and that the iliac index derived from combination of these angles is a good indication of the presence of mongolism at birth and a better one when the child has grown to six months of age. Although these findings are based upon study of only 19 mongoloid children, the magnitude of the differences observed endows them with statistical significance of a high order.

Current information on a new disease entity, hypophosphatasia, has been assembled by Lanman (92). In spite of the many postulated functions of alkaline phosphatase, its congenital absence has thus far been associated only with defects in new bone formation yielding clinical evidence of rickets. Additional study will be necessary to exploit fully the opportunities offered by this unusual defect for dissecting the normal metabolic role of alkaline phosphatase. An interesting single case study (93) describes craniostenosis, abnormal bone growth, and premature exfoliation of deciduous teeth in a child with normal calcium and phosphorus but consistently low alkaline phosphatase blood levels. Duodenal juice and liver tissue removed at biopsy had normal enzyme activity. Bone biopsy from the skull was lacking in phosphatase activity demonstrable by histochemical methods, yet osteoblasts grown from this specimen in tissue culture produced the enzyme in normal amounts. No inhibitors were found in blood serum.

Further discussion of hypertonic dehydration is offered by Finberg (94) and by Weil (95). The clinical association of profound central nervous system disturbances during acute infantile diarrhea should alert the physician to the possibility that water loss has exceeded electrolyte loss. The diagnosis is readily made by determination of serum sodium, potassium, and chloride. Such infants have an increase in spinal fluid protein and many suffer irreversible cerebral damage. Recognition of the high sodium levels calls for gradual restoration of the water loss with hypotonic solutions and later correction of potassium and calcium deficits.

Gruskay & Cooke (96) found higher levels of egg albumin in the serum after a standardized dose among infants who were recovering from diarrhea than among controls. A quantitative precipitin test was used for the serum analysis. Increased intestinal permeability seemed to be a more likely ex-

planation for the phenomenon than a reduction in the rate of destruction or excretion from the blood stream. The authors feel that infants in the post-diarrheal state may be temporarily vulnerable to sensitization by ingested proteins and recommend convalescent feeding with protein-free substances until the inflammatory reaction in the mucosa has abated.

The results of a two year study of sudden non-traumatic death in infants (97) exonerate thymus gland hypertrophy and suffocation as explanations of this tragic accident, but offer no comprehensive alternate pathogenesis. Minor degrees of inflammatory reaction in various parts of the respiratory tract and hemorrhagic pulmonary edema were found in a high percentage of the subjects. Bacteriologic studies of the blood and viral studies of various organs gave no consistent abnormal findings. The possibility of an immature immunologic defense is suggested but no gamma globulin determinations are reported.

In reporting nine examples of fibrocystic disease of the pancreas with paradoxically normal or partial pancreatic function, di Sant'Agnese (98) philosophizes about the nature of the disease. Of the cardinal manifestations (pancreatic insufficiency, obstructive pulmonary emphysema, abnormal sweat electrolytes, and positive family history) the most constant is abnormal sweat which in the author's experience occurs in 99 per cent of the cases studied. Its further significance is attested by the detection of abnormal electrolyte patterns in the sweat of parents and siblings of affected children even though these relatives may be otherwise well. Pancreatic insufficiency is present in over 90 per cent of the individuals studied, and in the remaining 10 per cent, later deterioration of pancreatic function may occur. Pulmonary pathology can occur in the absence of pancreatic insufficiency. The disease is viewed as a widespread disorder of exocrine and mucus-secreting glands. The author champions retention of the name cystic fibrosis of the pancreas in spite of its incomplete aptness. Richmond (99) offers another diagnostic test in the determination of chymotrypsin in duodenal juice. A statistically significant depression of average birth weight was found in a survey of the records of the Sloan Hospital (100) among infants who later were found to suffer from cystic fibrosis of the pancreas. Fetal or maternal metabolic factors are presumed to be accountable for this phenomenon.

Boyer & Andersen (101) traced the pedigrees of 50 children with known celiac disease and found a significant incidence of the same disorder among relatives of the propositi together with an increase in recurrent diarrhea and food intolerance. No association with diabetes was uncovered. The pedigrees were controlled by similar investigation of the pedigrees of children of members of the hospital resident staff.

The experience of the Children's Medical Center with cirrhosis of the liver and portal hypertension is analyzed by Craig, Hsia & Gellis (102, 103). Nearly one hundred cases have been seen over the 30 year period included in the study. Exactly half were sequelae of congenital atresia of the bile ducts;

another 30 per cent followed hepatitis, either neonatal, viral, or asymptomatic. Ultimate prognosis is very poor since the only survivors were seven patients in the groups with virus or asymptomatic hepatitis. Portal obstruction may occur in the presence of cirrhosis or apart from it. Valvular anomalies, or scarring, atrophy, and thrombosis of the portal vein presumably due to neonatal infection, account for the non-cirrhotic forms of portal obstruction. Once discovered, some type of operative relief is mandatory since without intervention recurrent and ultimately fatal bleeding from varices occurs. Splenorenal shunt is preferred in children to portacaval anastomosis.

In summarizing the results of a four and a half year study of hormone therapy of nephrosis, Heymann and his colleagues (104) draw some cautious conclusions. Although a high percentage responded with diuresis and at least temporary symptomatic relief, they view their ultimate mortality of around 35 per cent as not significantly different from the results obtained before the use of hormones was begun. Among the one-quarter of their patients already dead, they cite several treated early in the disease who lived less than a year. Failure to respond to hormones or the occurrence of convulsions early in the disease are regarded as poor prognostic signs. The metabolism of plasma proteins in nephrotic children has been studied by Gitlin, Janeway & Farr (105). Human plasma albumin, gamma globulin and iron-binding globulin were injected intravenously into children with nephrosis in various clinical stages. Rates of disappearance and of excretion in the urine were followed and by a series of involved calculations, the conclusion is reached that in the nephrotic child the rate of protein synthesis is at the upper limit of normal, not markedly increased as some have postulated. Low plasma levels are due to the increased urinary losses and an increase in the rate of catabolism.

Wedgwood & Klaus (106) traced and restudied 26 children who were well following anaphylactoid purpura. Most of the subjects were over two years past the onset of their initial disease. Particular attention was directed at the kidney and in ten of the 26, microscopic hematuria and cylindruria were found with the Addis technic. In general, evidence of renal functional impairment was absent or doubtful. The authors suggest that this disorder may be an antecedent of chronic nephritis seen in later life.

The character of subdural fluid in respect to its protein content has been examined by Gitlin (107). An increased ratio of albumin:gamma globulin in the fluid compared to the simultaneously determined values in the individual's serum, leads the author to the conclusion that subdural fluid is a transudate from damaged blood vessels of the meninges. He argues against the old concept that the fluid is derived from the oncotic pressure of protein during the breakdown of a subdural hematoma.

Bush (108) reviewed the role of trace elements in hemopoiesis in animals and man. Although copper deficiency in animals is a well known cause of anemia, similar deficiency in man has only recently been recognized. Low

blood levels of copper have been found in nephrosis, sprue, and Wilson's disease. In nephrosis, the explanation appears to lie in renal loss of ceruloplasmin. In the more recently recognized entity described by Lahey & Schubert (109), anemia is associated with hypocupremia, hypoferremia, and reduction in plasma proteins including iron-binding globulin. No renal losses of copper were demonstrated. Dietary therapy readily corrected the anemia.

Tuberculosis

The proceedings of an international conference on tuberculosis in childhood held at the National Jewish Hospital in Denver have now been published (110). Opening the conference with a synoptic view of the problem, Dubos decries any smugness about the conquest of tuberculosis, pointing out that even in such a favored country as the United States there is still ten times as much morbidity and mortality from this cause as from poliomyelitis. He emphasizes the importance of childhood tuberculosis by stating that the ultimate rates of morbidity and mortality for any generation are determined by the extent to which that generation becomes infected in early life. Four general methods of control are outlined with brief consideration of the unsolved problems of each. First, the elimination of exposure to tuberculosis would be the ideal method of control. For many areas of the world this is an impossibility at present. Second, through a clearer understanding of those physiologic factors which permit the school-age child to defend himself successfully against a primary invasion of the disease, it might be possible to increase non-specific resistance. Unfortunately these factors are but poorly understood. Third, artificial induction of specific resistance has been demonstrated with BCG vaccination, but the degree and duration of immunity cannot be measured because of the lack of a proper test. The tuberculin reaction measures sensitivity but has no necessary relation to immunity. Fourth, chemotherapy or chemoprophylaxis of tuberculosis may succeed in eliminating or suppressing the bacilli but does not necessarily result in enduring immunity. Used early after exposure it may prevent invasion or kill off organisms which have entered the tissues in too small numbers to stimulate an immune response. Used later in the course of infection, it may halt proliferation of bacilli in the tissues yet leave viable organisms as the seed of recrudescence in later life. Only a few of the many papers of the symposium which bear upon these major problems can be mentioned.

Ustvedt describes the usual and unusual pathologic consequences of BCG vaccination. In addition to local ulceration, lupus, lymphangitis and adenitis, generalized dissemination of organisms has been discovered in vaccinated individuals dying of other causes. Metastatic lesions are ordinarily free of viable organisms, but in at least four, well-studied cases progressive and fatal BCG infection has occurred.

Ström has worked out a rough test of immunity. By labeling BCG

organisms with P^{32} he is able to follow the rate of their diffusion from the site of injection into the lymphatic system and to gauge the speed of their destruction by the recovery of P^{32} in the urine. Immune animals and human subjects contain the injected bacilli locally and may excrete radioactive phosphorus within an hour. In non-immune subjects the diffusion of the organisms is more rapid and the excretion of phosphorus delayed. He concludes that oral vaccination with BCG is an uncertain method. Extending his remarks to the general question of BCG vaccination, Ström refers to a recent article by Wallgren (111) in which the need for mass vaccination is re-evaluated. Now that miliary, meningitic, and even primary tuberculosis have been suppressed to a vanishing level in Scandinavia, Wallgren believes that continuance of the mass vaccination program is no longer necessary. He favors vaccination of hospital personnel and of children in families with a risk of exposure and urges mass vaccination of populations which still have high rates of infection.

The supremacy of isoniazid in the chemotherapy of tuberculosis is attested by the preoccupation of both the clinicians and the experimentalists with its action. Several papers deal with the phenomenon of isoniazid-susceptible organisms persisting in the tissues in spite of the presence of high blood levels of the drug. McDermott describes a biologic mystery in his experiments with mice infected intravenously. After a period in which the infection is allowed to gain a foothold sufficient to produce lesions, heavy treatment with pyrazinamid and isoniazid is given to the animals. "Sterilization" of the tissues can be achieved if the proper sequence and time intervals are used. By "sterilization" is meant the inability to find tubercle bacilli in any of the tissues by culture, animal inoculation, microscopic examination, or a delayed examination after prolonged incubation. But if the animals are similarly tested 90 days after the termination of treatment, about one-third of them will have viable and isoniazid-susceptible organisms in their tissues. How the bacilli are sequestered constitutes the mystery. During the symposium, recurrent reference is made to the analogous phenomenon in human infection wherein the patient whose disease appears to be responding well to therapy continuously or intermittently excretes viable isoniazid-susceptible organisms. From experimental evidence, several discussants believe that the tubercle bacilli enter a stage of hypometabolism during which they fail to take up the drug and thus are able to survive in its presence. This explanation is favored over the theory that they are shielded from the drug by residence in caseous lesions from which they are periodically extruded.

The superiority of isoniazid to streptomycin in the treatment of tuberculous meningitis is affirmed by declining mortality rates from several clinical centers. Regimens of treatment vary widely depending upon the concept of underlying pathology. Debré, for instance, is content to use oral isoniazid and aminosalicylic acid for patients diagnosed early, reserving streptomycin and other measures for comatose subjects. Cocchi, on the

other hand, is so concerned about the adverse effects of allergic inflammatory reaction in the formation of protective granulomata and arachnoid adhesions that he subjects all of his patients to a complicated routine of parenteral antibiotics and intrathecal streptomycin and hydrocortisone. He cites an impressive record of 97 per cent complete cures in his last 38 cases.

Several presentations deal with the problem of endobronchial tuberculosis in the young child in which adherent mediastinal nodes compress the bronchial wall leading to emphysema, atelectasis, and bronchiectasis. Traditional chemotherapy appears to have little effect upon the speed of recovery from this form of tuberculosis. Bronchoscopic examination and drainage of secretions is advocated by some, and Laff even suggests that rupture of caseous nodes into the bronchus should be encouraged as the most rapid pathway of resolution. Though infrequently fatal, this form of tuberculosis is usually protracted and may result in permanent structural damage to the lung.

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